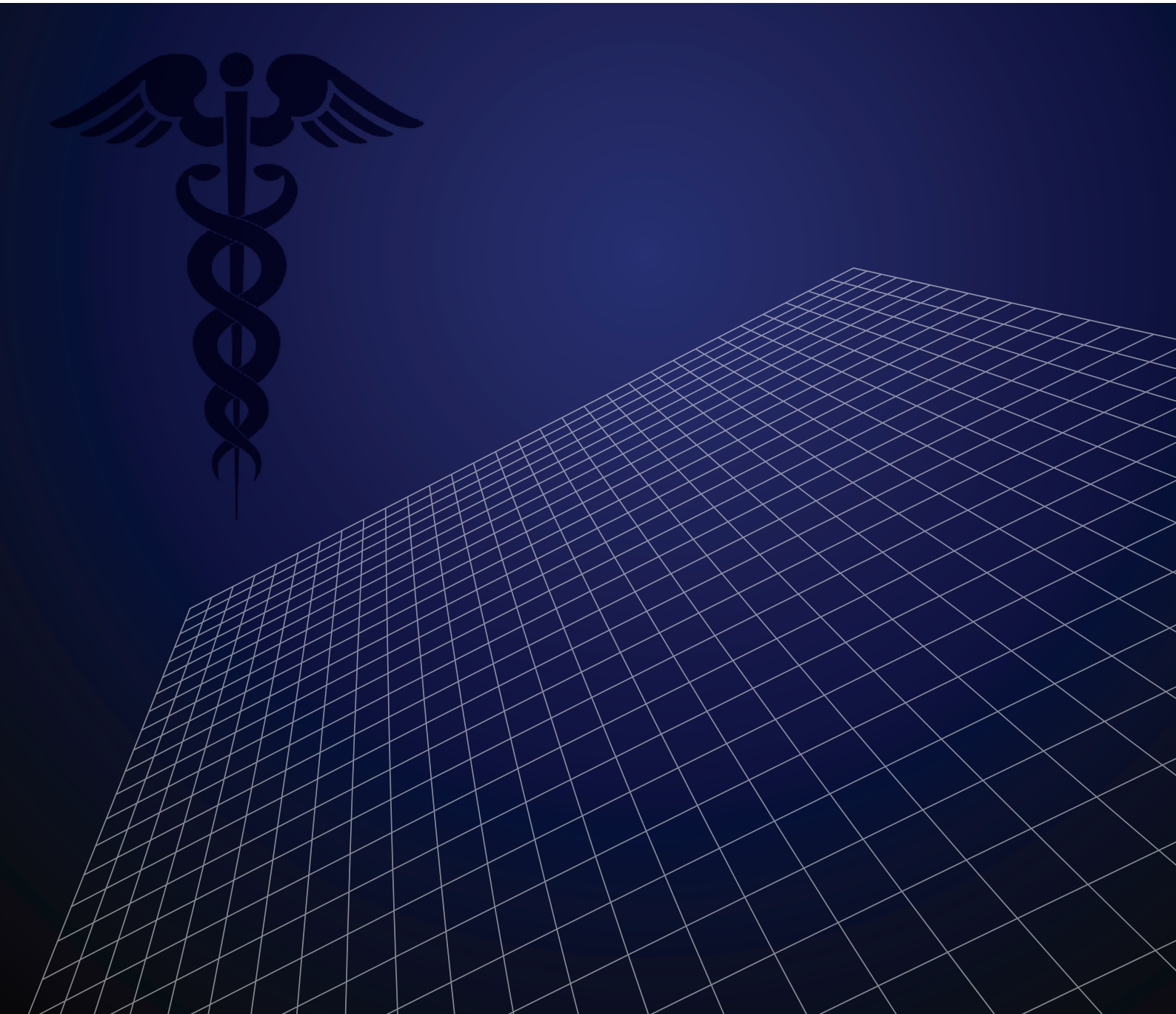
e-ISSN: 2149-8296

Turkish Journal of Clinics and Laboratory

Türk Klinik ve Laboratuvar Dergisi

Eylül 2020, Cilt:11 Sayı:4



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TURKISH JOURNAL of CLINICS and LABORATORY
Eylül 2020, Cilt: 11, Sayı: 4 Üç Ayda Bir Yayımlanır

Makale gönderim adresi: http://dergipark.gov.tr/tjcl/

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Turkish Journal of Clinics and Laboratory

To cite this article: Menekse S. Achievement rate and complications of comminuted ıntra-articular distal radius fracture treatment by means of closed reduction and use of external fixator. Turk J Clin Lab 2020; 4: 214-219.

Original Article

Achievement rate and complications of comminuted ıntra-articular distal radius fracture treatment by means of closed reduction and use of external fixator

Eklem içi distal radius kırıklarında kapalı redüksiyon ve eksternal fiksatör kullanılarak yapılan tedavinin başarı ve komplikasyon oranları

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Abstract

Aim: Distal radius fracture extending into the joint is very common; in any case, the administration of this fracture is controvertible. Related to the significance of intra-articular fracture of the distal radius and the best treatment strategy for the fracture, we tried to evaluate the achievement rate following the treatment of comminuted intra-articular fracture of the distal radius by means of closed reduction and utilization of external fixator.

Material and Methods: This retrospective study was taken over at our division of orthopedics by means of appraisal of radiographs and patient documents of those overlook from 2016 to 2018. We randomly allocated 41 patients treated surgically with bridging external fixation. İnformations administered the DASH quality-of-life questionnaire at postoperative months 6 and 24, performed functional assessment of pain, range of motion, and palm grip strength, and radiographic examinations (volar and radial angle, and height of the radius) before the operation, immediately afterwards, and at 3 and 12 months postoperative. Information were evaluated SPSS 18 programming and were exhibited as mean ± standard deviation (SD). The essentialness level was set at $P \leq 0.05$.

Results: Generally: 28% of the patients was seen ≤ 2 mm shortening of the radius, 53% of the patients had 2- 5 mm outspread shortening and 19% of the patients had in excess of 5 mm shortening of the range. Most of the members patients had admissible results. The mean average angulation was 6.28 ± 2.85 degrees and the average shortening was 3.92 ± 2.22. %39 percent of the patients had shortening of under 5 mm, 56% had shortening of 5- 10 mm and 5% in excess of 10 mm shortening, individually.

Conclusion: The aftereffects of our examination demonstrated that the smaller than expected external fixator is a decent and viable treatment alternative for acquiring outspread length, angulation and hard association in intra-articular fracture of the distal radius.

Keywords: Closed Reduction, İntra-Articular Fracture, Distal Radius Fracture, External Fixator

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Recevied: 09.12.2019 accepted: 06.07.2020
Doi: 10.18663/tjcl.657375

Öz

Amaç: Eklem içine uzanan distal radius kırığı çok yaygındır; birçok tedavi yöntemi mevcuttur. İntra-artiküler distal radiusun parçalanmış kırığının önemini ve bu tarz kırıklar için en iyi tedavi stratejisi ile ilgili olarak, kapalı redüksiyon ve eksternal fiksatör kullanımı ile tedavisinin başarısını ve komplikasyon oranlarını değerlendirmeye çalıştık.

Gereç ve Yöntemler: Bu retrospektif çalışma, 2016'dan 2018'e kadar Ortopedi kliniğimizde tedavi edilen hastaların radyografileri ve hasta dosyalarının değerlendirilmesi ile yapıldı. Eksternal fiksasyon köprüleme ile cerrahi olarak tedavi edilen 50 hastayı rastgele ayırdık. Bilgiler 6 ve ameliyat sonrası 24. ayda DASH yaşam kalitesi anketi uygulandı ve kavrama gücü palm ve operasyon öncesi yarıçap (volar ve radyal açı ve yükseklik) radyografik muayeneler, hemen sonra, 6 ve 24 ay ameliyat sonrası ağrı, hareket açıklığı, fonksiyonel değerlendirme yapıldı. Sonuçlar SPSS 18 programında değerlendirildi ve ortalama ± standart sapma (SD) olarak gösterildi. Anlamlılık seviyesi $p \leq 0.05$ olarak belirlendi

Bulgular: Hastaların %28'inde ≤2 mm yarıçapın kısalması, %53'ünde 2-5 mm arasında kısalması ve %19'unda 5 mm'den fazla kısalma görüldü. Hastaların çoğunluğunun kabul edilebilir sonuçları vardı. Ortalama angulasyon 6.28 ± 2.85 derece ve ortalama kısalma 3.92 ± 2.22 mm idi. Hastaların %39'unda 5 mm'nin altında kısalma, %56'sında 5 - 10 mm kısalma ve %5'inde 10 mm'yi aşan kısalma vardı.

Sonuç: Çalişmamızın sonuçları intra-artiküler distal radius kırığının eksternal fiksatör tedavisinin beklenden daha az olsada angülasyon, radial kısalma gibi sonuçalar açısından alternatif iyi bir tedavi seçeneği olduğunu göstermiştir.

Anahtar kelimeler: Kapalı redüksiyon, İntra-artiküler kırık, Distal radius kırığı, Eksternal fiksatör

Introduction

Contains roughly 16% of all fracture treated by orthopedic specialists distal radius fracture is the most widely recognized fracture of the lower arm [1] . This fracture was clinically analyzed in 1814 by Colles, who depicted this element in a paper distributed in Edinburgh [2]. The standard sequence of posterior-anterior (PA), lateral and oblique radiographic perspectives are helpful to envision associated fracture with the distal radius. In 1993, Fernandez proposed a component based order framework that tended to the potential for ligamentous damage and treatment suggestions (type I-V) [3][4] Intra-articular distal Radius fracture present to high [5]-vitality, unpredictable, unstable wounds . The ideal treatment of which stays a subject of discussion. A wide range of treatment techniques have been pushed, including external fixation, open reduction and internal fixation with K-wires, dorsal plating and palmar plating. The objective of treatment of these fracture is a wrist that gives adequate painless movement and stability to allow professional and avocational exercises for all age bunches without the affinity for future degenerative changes in the youthful [6][7]There have been numerous ongoing advances both in careful systems and in equipment plan [8] A few investigators have supported the utilization of smaller than expected use fixators in the treatment of comminuted intra-articular fracture of the distal radius with various and fairly opposing achievement rates [9]

Regardless of the significance and predominance of distal radius fracture, there are inadequate examinations and conflicting outcomes, in this manner we chose to survey the achievement pace of comminuted intra-articular fracture of distal radius treated by means of closed reduction and external fixator assess entanglements and results.

Materials and methods

This study was approved by Adana City Hospital Ethical Committee. There is no conflict of interest

This longitudinal review study was led evaluating radiographic outcomes and graphs of patients with comminuted intra-articular fracture of distal radius treated via closed reduction and external fixator from 2016 to 2018. The subjects were patients with comminuted intra-articular fracture of the distal radius treated via closed reduction and external fixator. Rejection criteria included extra-articular fracture or pathologic fracture causes of tumors and other diseases.

There was independent assessment of the DASH questionnaire, functional and radiographs outcomes. All assessors were not blinded. The sample size was calculated beforehand, taking a confidence interval of 95%, statistical power of 90%, standard deviation of 15% in the DASH scores, and an absolute difference of 10% on DASH scores between Pinning and External Fixator. All study participants were evaluated at 6 and 24 months after surgery. The assessor outcomes asked them to fill the DASH

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questionnaire. To assess pain in the affected wrist, the assessor outcomes asked to participants to use a visual analog scale (VAS) in which pain level was expressed as an absolute value [10].

We chose subjects dependent on the Poisson model 41 subjects were surveyed. Schanz pins were set in second metacarpal bone Schanz pins were set in the distal radius.

Radiographic criteria were surveyed and recorded by a similar radiologist. These criteria included: level of angulation (diminished size from the typical span edge in degrees), shortening of the range bone (diminished size from the ordinary sweep length in millimeters) and dorsal/palmar tilt. Patients were pursued for in any event a half year relying upon their clinical conditions. The achievement pace of the treatment was resolved dependent on the length of the sweep after treatment as: great (shortening ≤ 2 mm), satisfactory (2- 5 mm) and awful (shortening> 5 mm). Moreover, the achievement pace of treatment was resolved as per the level of angulation as: great (angulation <5 degree), adequate (5-10 degrees) and awful (angulation> 10 degree).

At 3 and 12 months after the operation, all patients underwent bilateral objective functional assessment consisting of goniometry and dynamometry by two independent physiotherapists. In the goniometric evaluation, the pronation-supination of the forearm, flexion-extension of the wrist and ulna, and radial deviation of the wrist were measured. Wrist grip strength was assessed using the Jamar® dynamometer. The results were expressed as the difference in values between the uninjured and affected sides (index of limitation). The functional and radiographic evaluations, pain measurements using the VAS, and applications of the DASH questionnaire were performed by professional orthopaedists and physiotherapists who were not directly associated with the study.

Ethics Approval

The study was approved by Adana city hospital ethic committee.

Statistical Analysis

The information was surveyed through the SPPSS rendition 18 programming. Distinct examination of quantitative and subjective information was performed, and the outcomes were introduced as mean ± standard deviation (SD) and recurrence, separately. Additionally, relative and binomial tests were utilized to think about radiographic results of treatment. Calculated relapse was utilized to control puzzling factors. Criticalness level was set at $P < 0.05$.

Results

Out of 41 patients, 24 (58.5%) were males and 17 (41.5%) were females. The mean age of the patients was 48.26 years with a scope of 18-75± 14.78 years. The main additional pathology was DM, which was found in 4 (9.7%) patients. In view of the Fernandez classification of the distal Radius fracture, 12 (29%) of the subjects had type II fracture, 16 (39%) had type III, 12 (29%) had type IV and three (7%) had type V fracture. It was seen that 8 (17%) of the patients had an open fracture and 33 (83%) of them had a closed fracture. Besides, 11 (26.8%) of the patients had shortening of the radius ≥ 2 mm, 13 (31.7%) had 2-5 mm spiral shortening and four (9.7%) of the patients had in excess of 5 mm shortening of the radius

The base angulation was zero degree and the maximum were eleven degrees; the mean was 5.64 degrees. As shown in Figure 1 complications rate, we could say that the treatment was acceptable. The radial shortening in patients with kind II fracture was 3.56 ± 2.47 mm. The Patients with kind III fracture had radial shortening with a mean of 4.21 ± 1.56.the patients with kind IV fracture had a mean of 3.98 ± 1.86 mm and the others with kind V fracture had shortening of 4.22 ± 2.76 mm. The mean outspread shortening in the patients was 3.86 ± 2.08 mm (Table 1).

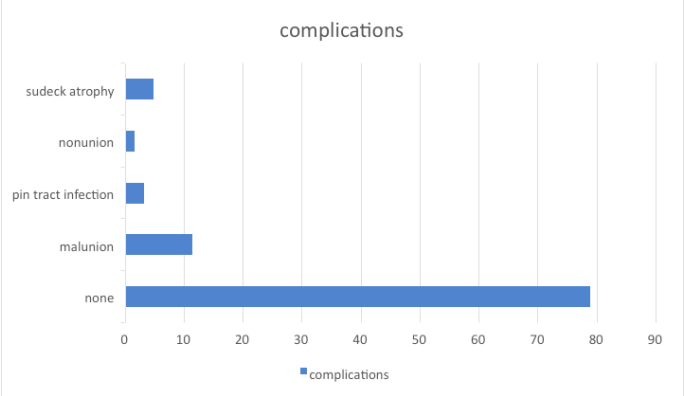

Figure 1: [rate of complications]

Table 1: [Shortening of the Radius based on fracture type]

Fracture type	Number of patients (a)	Values (b)
2	12(29)	3.56 ± 2.47
3		4.21 ± 1.56
4	12(29)	3.98 ± 1.86
5	1(3)	4.22 ± 2.76
Total	41	3.86 ± 2.08

[a data is presented as mean ± SD, b data are presented as no (%)]
SD: Standard deviation

Patients with kind II fracture had a mean spiral angulation of 4.78 ± 1.56 degrees while those with kind III had a mean angulation of 5.98 ± 2.26 degrees. Those withkind IV fracture had a mean of 6.78 ± 2.58 degrees and the subjects with fracture kind V had a mean angulation of 9.18 ± 3.59 degrees. The mean angulation of the range for the whole gathering was 5.79 ± 1.96 degrees (Table 2).

Table 2: [Angulation]		
FRACTURE TYPE	NUMBER OF PATİENT	VALUES
2	12(29)	4.78 ± 1.56
3	16(39)	5.98 ± 2.26
4	12(29)	6.78 ± 2.58
5	1(3)	9.18 ± 3.59
TOTAL	41	5.79 ± 1.96

The mean angulation for patients with open fractures was 6.98 ± 2.25 degrees and for those with closed fractures, this was 6.05 ± 2.52 degrees(P>0.05). The mean radius shortening for patients with open and closed fractures was 4.97 ± 2.86 mm and 3.27 ± 1.68 mm, respectively (P>0.05). No statistically significant differences were observed in these results.

These discoveries demonstrated no noteworthy by means of the chi-square test (P-estimation of 0.76). To confirm the relationship between open or closed fracture and the event of difficulties, we broke down these factors by means of the chi-square test. Be that as it may, measurably significant contrasts were not watched (P>0.07).

Results after 3 and 12 months with regard to functional limitation (DASH), compared with patients treated with the external fixator. However, this finding only reached statistical significance for evaluation using the DASH questionnaire after 3 months, of follow-up (mean difference =-7.1 p = 0.044) (Table 3). There were no statistical differences between two groups when pain scores (VAS) were assessed. (Table 3).

Table 3: outcomes 1	
	outcomes
3. months	
DASH score	22,8
VAS score	2,9
12.months	
DASH score	11,8
VAS score	1,2
DASH- percentage values for limb limitation: low values indicate less limitation VAS-Visual analogue scale:low values indicate less pain	

Comparative analysis of the grip strength limitation index (uninjured side minus affected side grip strength) showed similar results for the two groups at both 6 and 24 months after surgery (Table 4).

Table 4: Mean limitation Radyocarpal joint in degrees	
	outcomes
3. months	
Flexion	19,6°
Extension	20,7°
Ulnar desviation	8,6°
Radialdesviation	5,7°
Pronation	17,1°
Supination	17,6°
12. months	
Flexion	5,4°
Extension	4,3°
Ulnar desviation	2,5°
Radialdesviation	1,8°
Pronation	3,3°
Supination	4,4°
* Units of measurement = degrees	

Analysis of the range-of-motion limitation index showed a statistical difference (p = 0.043) favouring the external fixator group with regard to the supination movement 6 months after the operation; however, this was not maintained at 24 months. For all other measurements, the results were similar between the groups (Table 4).

Discussion

Intra-articular distal radius fracture speaks to high-vitality, perplexing and unsteady wounds; the ideal treatment of which stays a theme of discussion. A wide range of treatment techniques have been proposed including, external fixation, open reduction internal fixation with K-wires, dorsal plating and palmar plating [5] There have been numerous ongoing advances both in careful strategies and in instrument plan. A few driving specialists have bolstered the utilization of smaller than expected outer fixators in the treatment of comminuted intra-articular fracture of the distal radius [15] . The majority of the fracture in youthful cases were brought about by street auto collisions [16] .Distal Radius fracture is one of the most widely recognized wounds, and as time has passed by, an ever increasing number of orders have developed with the rise of progressively novel and successful treatment choices that incorporate a cast, external fixasion, percutaneous pinning, or K-wire fixation and bone grafting. It tends to be said that,

every one of these modalities intend to acquire ideal radial length and radial inclination affirmed by taking pre and post-usable radiographs [17] .

İnternal and external are both widely used in clinic distal radius fracture. A large amount of trials, among them, some were RCTs whereas some were not, investigated the difference of IF versus EF in the treatment of distal radial fractures; however, no consensus were reached. Therefore, more recently, a series of overlapping meta-analyses were conducted to further explore this issue by pooling relevant studies. Unfortunately, homogenous conclusion was still unavailable. Up to now, with regard to the evidence for the treatment opinions of DRF, the recommendation summary of the American Academy of Orthopedic Surgeons clinical practice guideline was 'inconclusive' [11].

Main functional outcomes used in these studies including Disabilities of the Arm, Shoulder and Hand (DASH) score and grip strength. DASH score is a self-reported questionnaire used to assess upper extremity function ranging from 0 point (no disability) to 100 points (maximum disability).44 All included meta-analyses used DASH scores as the primary outcome. Except the 2 selected meta-analyses, there were another five[12][13] ones revealed lower DASH scores obtained in the IF group at 1 year follow-up. Meanwhile, Wang et al[14] also reported better DASH scores at 3 months and 6 months follow-up in the IF group, and after excluding patients who did not use VLP, the results were even more favorable. One most possible explanation for this difference of DASH scores is that plate osteosynthesis could better restore the bony anatomy as a stable internal fixation and therefore allow patients to have an early and active mobilization regimen. No included meta-analyses showed difference of IF and EF in the rehabilitation of grip strength.

In the same way as other different investigations, in our examination a large portion of the members were; the male/female proportion was 1.38/1. The mean radial angle in our examination was 5.79 ± 1.96 mm while Arshad et al. [18] announced a radial inclination angle 12.52 ± 2.59 mm. In this way, it appears that deviation from a typical point in our examination was less. In the investigation of Jenkins et al. [19] , radial angulation after treatment in patients with Colles fracture in the lower arm plaster and external fixator gathering radial inclination were 6.5 ± 5.2 and 0.7 ± 3.9 degrees, individually. The discoveries demonstrated that radial shortening was 3.7 ± 2.8 mm in patients with lower arm plaster and 0.3 ± 1.8 mm for those with external fixator. Our outcomes were higher than what was accomplished by Jenkins et al. [19] likewise connected to aftereffects of radial angulation. This distinction may emerge from fracture contrasts. Additionally, pin tract disease was seen in a few patients like our investigation. Melone et al. [20] considered the use of external fixator use in the treatment of intra-articular fracture of the distal angle and detailed 3.2 mm radial shortening, which is like our discoveries. Type IV (34.78%) fracture was the most successive type, in the investigation of Jakim et al. [21] regarding seriousness, nonetheless, in the present investigation, the most well-known fracture was type III (35%). This distinction could be because of the seriousness of fracture and the instrument that they used. The radial lengths were additionally better in the referenced examination. The distinction in the aftereffects of Krishnan [22] and the present examination might be because of the consideration of comminuted fracture in the present investigation.

Conclusion

Succesful of the trrathment of distal Radius fracture associated with lower DASH scores, better rehabilitation of volar tilt and radial inclination, and lower infection rates at 1 year postoperatively. The aftereffects of our examination demonstrated that the smaller than expected external fixator is a decent and viable treatment alternative for acquiring outspread length, angulation and hard association in intra-articular fracture of the distal radius.

Comminuted intra-articular distal radius fracture represent to a troublesome issue for orthopedic specialists [23] . We feel the treatment used in this investigation was effective, treatment by means of closed reduction and mini external fixation was satisfactory. In any case, it is related with certain difficulties that require cautious pin site the board and legitimate patient choice. We can use external fixator for unstabil distal Radius fracture.However, further investigations are still needed to warrant current conclusions.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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To cite this article: Terzi E. Alopesi areata ile serum 25(OH) d vitamini ilişkisi. Turk J Clin Lab 2020; 4: 220-224.

Orijinal Makale

Alopesi areata ile serum 25 (OH) D vitamini ilişkisi

Association between 25 (OH) vitamin D and alopecia areata

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ÖZ

Amaç: Alopesi areata (AA) hastalarında serum 25-hidroksivitamin D (25 (OH) D) seviyelerini incelemek ve sağlıklı bireylerden oluşan kontrol grubu ile karşılaştırarak serum 25 (OH) D seviyeleri ile AA arasında olası bir ilişki olup olmadığı belirlemektir.

Gereç ve Yöntemler: Ekim 2017-Mart 2018 tarihleri arasında AA tanısı konulan 43 hasta ve 69 sağlıklı birey çalışmaya alındı.Çalışma grubunun serum D vitamini düzeyleri yüksek performans likit kromatografi yöntemi ile değerlendirildi. Ayrıca serum kalsiyum, fosfor, alkalen fosfataz ve paratiroid hormon seviyeleri de değerlendirildi.

Bulgular: Çalışmamıza 10-47 yaş(ortalama: 33.41 ± 7.2) arasındaki 43 hasta ve kontrol grubunda 18-55 yaş arası(ortalama: 33,53 ± 7.2). 69 sağlıklı birey katılmıştır. AA'lı hastalarda serum 25 (OH) D seviyeleri ortalama 20,21 ng / ml (3,7-43,5 ng / ml) olarak belirlendi. Kontrol grubunda ise serum 25 (OH) D seviyeleri ortalama 24,09 ng /ml(3-69,2 ng / ml) olarak belirlendi.. Her iki grup arasında serum D vitamini düzeyi arasında istatistiksel olarak anlamlı bir fark yoktu(p> 0.05).

Sonuç: Bu sonuçlar ışığında AA ile serum 25(OH) D vitamini arasında herhangi bir ilişki saptanmamıştır.

Anahtar kelimeler: Alopesi areata; 25(OH) D vitamini; likit kromatografi

ABSTRACT

Aim: To evaluate the status of serum 25-hydroxyvitamin D(25(OH)D) in patients with AA,serum 25(OH) D concentrations were compared with AA patients and healthy controls and thus determine if a possible association exists between serum 25(OH) D levels and AA.

Materials and Methods: The study comprising 43 patients diagnosed with AA and 69 healthy controls was conducted between October 2017 and March 2018.The serum vitamin D levels of the study group were determined by high performance liquid chromatography.Serum levels of calcium,phosphorus,alkaline phosphatase, and parathyroid hormone were also evaluated.

Results: The study was based on 43 patients aged between 10 and 47 (mean:33,41±7,2).The control group included 69 healthy persons aged between 18 and 55 (mean:33,53±7,2).Serum 25(OH)D levels in patients with AA ranged from 3,7 to 43,5 ng/ml with a mean of 20,21 ng/ml. Serum 25(OH)D levels in healthy controls ranged from 3 to 69,2 ng/ml with a mean of 24,09 ng/ml.There was no statistically difference in the serum vitamin D level between AA patients and healthy controls(p> 0.05)

Conclusion: In the light of these results, no relationship was found between AA and serum 25 (OH) vitamin D.

Keywords: Alopecia areata; 25(OH) Vitamin D; liquid chromatography

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Volume 11 Number 4 p: 220-224

Giriş

Alopesi areata (AA) T lenfosit aracılı dokuya özgü bir otoimmün hastalıktır. AA'nın kesin patogenezi tam olarak anlaşılamamıştır. Bununlaberaberson kanıtlarAA'nınsaçfolliküllerinhedefalındığı otoimmun bir hastalık olduğunu desteklemektedir.AA'da histolojik olarak saç folliküllerinin çevresinde ve içinde lenfosit infiltrasyonu görülmektedir.Ayrıca saç folliküllerı çevresinde ve içinde makrofajlar ve Langerhans hücreleri gözlenmiştir[1,2]. Alopesi areata bir otoimmun hastalıktır ve romatoid artrit, diabetes mellitus, multiple skleroz gibi birçok otoimmun hastalık düşük D vitamini seviyeleri ile ilişkilidir [3). D vitamini yağda eriyen steroid yapıdadır,deride 7-dehidrokolesterolden sentez edilir veya besinlerle vitamin olarak alınır. Hem doğal hem de uyarlanabilir bağışıklık sistemlerinin normal işlevine aracılık etmede rolü vardır ve çoğu dokuda yaygın olarak dağıtılan D vitamini reseptörüne(VDR) bağlanarak biyolojik etkilerini gösterir. D vitamini, otoimmüniteyi tetikleyebilecek veya şiddetlendirebilecek süreçlerde rol oynamaktadı [4,5] Çeşitli çalışmalar, D vitamini seviyelerinin, multipl skleroz,lupus erimatozis,tip 1 diabetes mellitus ve romatoid artrit dahil olmak üzere bazı otoimmün hastalıkların insidansı ve / veya ciddiyeti ile ilişkili olduğunu bildirmektedir[6-9]. Ayrıca topikal D vitamini analogları psoriazis ve vitiligo dahil kutanöz otoimmun hastalıkların tedavisinde etkilidir[10]. Çalışmamızın amacı AA'lı hastalarda D vitamini durumunu değerlendirmekti. Coğrafi alanımızdaki D vitamini eksikliği yaygınlığının yüksek olması nedeniyle, sağlıklı bir kontrol grubundaki seviyeleri de değerlendirdik ve Ekim 2017 ile Mart 2018 arasındaki iki grubu karşılaştırdık. Mevsimsel değişikliklerin D vitamini seviyeleri üzerindeki etkisini en aza indirmek için çalışma sonbahar ve kış aylarında gerçekleştirilmiştir.

Gereç ve Yöntemler

Hastalar

Bu çalışma, Ekim 2017-Mart 2018 tarihleri arasında İstinye Üniversitesi Liv Hastanesi , Dermatoloji Anabilim Dalında gerçekleştirilmiştir. AA'lı 43 hasta (29 erkek ve 14 kadın) ve 69 sağlıklı kontrol grubu (24 erkek, 45 kadın) retrospektif olarak incelendi. Oral D vitamini desteğine; majör kardiyovasküler, karaciğer, böbrek veya sindirim hastalığı olan; testten 1 ay önce AA tedavisi veya laboratuvar testini yapmayı reddedenler çalışmaya alınmadılar. Bölümdeki hasta görüşmeleri sırasında cinsiyet, yaş, AA başlangıç öyküsü, ana tutulum yeri, hastalığın süresi,ilerlemesi ve komorbid otoimmün hastalık öyküsü gibi hasta bilgileri kaydedildi. Lokal etik kurul onayı alındı. Hastalara onam formları imzalatıldı. Helsinki Deklerasyonu prensiplerine uyuldu.

Laboratuar Analizleri

25-hidroksivitamin D (25 (OH) D) , kalsiyum, fosfor, alkalin fosfataz (ALP) ve paratiroid hormonu (PTH) düzeylerini değerlendirdik. 25(OH) D vitamini düzeyleri 20 ng / ml den düşük ise eksik, 20-30 ng / ml arasında ise yetersiz ve 30 ng / ml den yüksek ise yeterli olarak değerlendirildi. Serum kalsiyum, fosfor ve ALP seviyeleri spektrofotometrik bir cihazla ölçülmüştür(Roche Integra 800). D vitamini yüksek performans likid kromatografi cihazı kullanılarak ölçüldü. Serum PTH seviyeleri kemilüminesans immünoanaliz cihazı (Siemens Centaur XP) ile ölçüldü.

İstatistiksel Analiz

Veri analizi SPSS , sürüm 11.5 (SPSS Inc., Chicago, Illinois, United States) programı kullanılarak yapıldı.. Sürekli değişkenlerin normal veya normal olmayan dağılımları Shapiro Wilk testi ile belirlenmiştir. Gruplar arasındaki ortalama farklar Student t-testi kullanılarak karşılaştırılmış, aksi takdirde medyan değerlerin karşılaştırılmasında bağımsız grup sayısına göre Mann-Whitney U veya Kruskal-Wallis testleri kullanılmıştır. Kruskal-Wallis test istatistiklerinden p-değeri istatistiksel olarak anlamlı olduğunda, hangi grubun diğer gruptan farklı olduğunu belirlemek için Conover'in parametrik olmayan çoklu karşılaştırma testi kullanıldı.Kategorik veriler Pearson'un χ2 testi veya Fisher's exact testi ile analiz edildi. Semptomların süresi ile D vitamini seviyeleri arasındaki ilişki derecesi düzeyleri Spearman'ın korelasyon analizi ile değerlendirildi. Olgu ve kontrol grupları arasında ayrım yapmak için en iyi belirleyiciyi saptamak amacıyla çoklu lojistik regresyon analizi uygulandı. Her bağımsız değişken için olasılık oranı ve% 95 güven aralıkları da hesaplanmıştır. P değerinin 0,05'in altında olması istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmaya 10-47 yaş aralığında (ort 33,41 ± 7,2) 43 (29 erkek, 14 kadın)hasta dahil edildi.Kontrol grubunda 18-55 yaş aralığında(ort 33,53± 7,2) 69 sağlıklı birey (24 erkek, 45 kadın) alındı. Hasta ve kontrol grubu arasında ortalama yaş açısından istatistiksel olarak anlamlı fark yoktu. 16(%37,2) hastada tek bir alopesik odak vardı ve 27 (%62,8)hastada birden fazla alopesik odak vardı.Lezyonlar kafa derisi ve sakal bölgesinde

yer almaktaydı (Tablo 1). AA olan 43 hasta arasında, ailede AA öyküsü yoktu.Hastaların 13'ünde(%30,2) Hashimoto tiroiditi ve 2 hastada(%4,6) tip 1 diabetes mellitus öyküsü vardı. Otoimmün hastalık 13 (% 30,2) hastada mevcuttu (Tablo 2).

Table 1. Hastaların ve kontrol grubunun demografik verileri.

	Hasta Grubu	Kontrol Grubu	P değeri
Yaş	33,41 ± 7,2	33,53± 7,2	0,942
Cinsiyet			0,425
Erkek	29(%67,4)	24(%34,8)	
Kadın	14(%32,6)	45(%65,2)	
Fitzpatrick Deri Tipi			0,681
Tip 2	7(%16,3)	10(%14,5)	
Tip 3	25(%58,1)	47(%68,1)	
Tip 4	11(%25,6)	12(%17,4)	
Vitamin D(ng/ml)	20,21(3,7-43,5)	24,09(3-69,2)	0,547
Vitamin D(ng/ml)			
>30	9(%20,9)	20(%29)	0,763
21-29	10(%23,3)	14(%20,3)	0,451
<20	24(%55,8)	35(%50,7)	0,438
<10	7(%16,3)	11(%15,9)	0,412
Kalsiyum	9,3±0,64	9,4±0,59	0,934
Fosfor	3,5±0,57	3,6±0,63	0,645
ALP	76,4±19,2	73,8±16,7	0,239
PTH	59,6±18,9	63,1±21,3	0,468

Tablo 2. AA'lı hastaların klinik özellikleri

Değişkenler	**Sonuçlar**
Hastalık süresi(Ay)	
<1	11(%25,6)
1-3	11(%25,6)
4-6	10(%23,2)
>6	11(%25,6)
Tutulum	
Tek lezyon	16(%37,2)
Birden fazla lezyon	27(%62,8)
Otoimmun hastalık birlikteliği	13(%30,2)
Haşimato Troidit	13(%30,2)
Tip 1 Diabetes Mellitus	2(%4,6)

AA'lı hastalarda serum 25 (OH) D seviyeleri ortalama 20,21 ng / ml (3,7-43,5 ng / ml) olarak tespit edildi.. Hastaların % 55,8'inde D vitamini eksikliği,% 23,3'ünde D vitamini yetersizliği ve % 20,9'unda yeterli D vitamini seviyesi vardı. Kontrol grubunda ise serum 25 (OH) D seviyeleri ortalama 24,09 ng /ml(3-69,2 ng / ml) tespit edildi.Kontrol grubunda ise deneklerin % 50,7'inde D vitamini eksikliği,% 20,3'ünde D vitamini yetersizliği ve % 29'unda yeterli D vitamini seviyesi vardı. Her iki grup arasında serum D vitamini düzeyi arasında istatistiksel olarak anlamlı bir fark yoktu(p> 0.05).Çalışma gruplarındaki kadın ve erkek oranı incelendiğinde, 25 (OH) D düzeyinde istatistiksel olarak anlamlı bir fark yoktu (p> 0.05).

10 ng/ml seviyesinin altında serum 25 (OH) D seviyeleri hastaların %16,3'ünde ve kontrol grubunun %15,9'unda gözlenmiştir.Her iki grup arasında istatistiksel olarak anlamlı bir fark yoktu (p> 0.05). Hastalar ve kontrol grubu arasında kalsiyum, fosfor, ALP ve PTH düzeyleri açısından istatistiksel olarak anlamlı fark yoktu(p> 0.05)(Table 2).

Tartışma

Saç folikülleri hormona karşı oldukça duyarlı bir organdır.[2]. D vitamini kalsiyum homeostazının düzenlenmesinde,hem hücre büyümesinde ve farklılaşma, ayrıca bağışıklık sistemi düzenlemesinde önemli bir rol oynayan bir hormondur[4, 5]. Biyolojik etkilere dayanarak, normal 25 (OH) D seviyesi ≥ 30 ng / dl'dir. D vitamini eksikliği, D vitamininin diyet alımındaki farklılıklar, güneş ışığına maruz kalma sürelerinin değişmesi veya takviyelerin kullanılması nedeniyle dünya çapında giderek daha fazla tanınmaktadır, D vitamini eksikliğinin yaygınlığı çeşitli popülasyonlarda farklı modeller göstermektedir. [11]. Çeşitli çalışmalar, D vitamini seviyelerinin, tip 1 diyabetes mellitus, sistemik lupus eritematozus, multipl skleroz ve inflamatuar barsak hastalığı dahil olmak üzere bazı otoimmün bozuklukların insidansı ve / veya ciddiyeti ile ilişkili olduğunu bildirmektedir[6]. Son çalışmalarda, D vitamini eksikliğinin AA oluşumu için önemli bir risk faktörü olabileceğini belirtilmiştir[12-15].

Yılmaz ve arkadaşlarının yaptığı bir çalışmada AA'lı hastalarda sağlıklı kontrollere kıyasla düşük serum 25 (OH) D seviyeleri saptandı[12]. Mahamid ve arkadaşları 23 hastayı kapsayan bir çalışmada AA ve D vitamini eksikliği arasında güçlü bir korelasyon bulmuşlardır[13]. Başka bir çalışmada Aksu ve ark., Serum 25 (OH) D düzeylerinin AA'nın hastalık şiddeti ile ters korelasyon gösterdiğini göstermiştir[14].156 AA'lı hasta ve 148 sağlıklı denekler üzerinde yapılan bir çalışmada, d'Ovidio ve ark., 25 (OH) D'nin yetersizliğinin veya eksikliğinin AA hastaları ve kontrol grubu arasında anlamlı olarak farklı olmadığını bulmuşlardır. Bununla birlikte, hastaların% 42,4'ünde 25 (OH) D eksikliği mevcuttu; bu, sağlıklı kontrollerde gözlenen% 29,5'ten önemli ölçüde daha yüksekti. Ek olarak, 25 (OH) D seviyelerinin azalması, saç dökülmesinin şekli veya boyutu ile ilişkili değildi [15].

Sonuçlarımız AA ve D vitamini eksikliği arasındaki ilişkiyi gösteren önceki raporlarla uyuşmamaktadır. Çalışmamızda hastaların 25 (OH) D eksikliği olduğunu bulduk, ancak AA

hastaları ve sağlıklı kontroller arasında serum D vitamini düzeyleri açısından istatistiksel olarak anlamlı bir fark yoktu. (p> 0.05). Bu, coğrafi alanımızda düşük 25 (OH) D değerlerine yönelik eğilimden kaynaklanıyor olabilir. Hekimköy ve ark., Türkiye'nin Ege bölgesinde yaptıkları populasyon temelli bir çalışmada yüksek bir D vitamini eksikliği (% 74,9) ve yetersizliği (%13,8) bulmuşlardır[16]. Türkiye'deki 1010 pediatrik hasta üzerinde yapılan bir çalışmada, Orun ve ark. 25 (OH) D eksikliğinin (% 24,3) ve yetersizliğinin çocuklukta, özellikle ergenlik döneminde sık olduğunu göstermişlerdir[17]. Van der Meer ve arkadaşları, Türkiye nüfusunda D vitamini durumunun Türkiye'de güneş koruyucu kullanımına,diyette D vitamini alımının yetersiz olmasına, daha koyu ten rengine ve vücudun çoğunu kaplamak için kıyafet kullanma alışkanlığına göre çok değiştiğini göstermiştir[18].

D vitamini güneş ışığı vitamini olarak bilinir. Bu vitaminin ana kaynağı D vitamininin derideki sentezidir. Çoğu insan için D vitamini ihtiyacının % 90'ından fazlası gündelik güneş ışığına maruz ile karşılanmaktadır. D vitamininin doğal diyet kaynakları sınırlıdır[19]. Güneşli iklimlerde yaşayan orta doğu popülasyonlarında, özellikle Lübnan, İran, Ürdün ve Türkiye'den gelen yayınlarda D vitamini seviyelerinin çok düşük olduğu bildirilmiştir. [20-22]. Bu durum, enlem, mevsimsellik, kirlilik, gümrük veya kültürel konular, diyet veya takviye edilmiş gıda politikaları gibi yaygın çevresel faktörlerden kaynaklanabilir. Ayrıca, bireysel giyim gibi sosyokültürel ve davranışsal faktörler, yüksek güneş koruma faktörü olan güneş kremlerinin kullanımı, güneşlenme alışkanlıkları, cilt pigmentasyonları, açık havada geçirilen zaman,ve yetersiz oyun alanları serum D vitamini seviyelerinin durumunu etkileyebilir.

Sonuç

Çalışmamızda hastaların 25 (OH) D eksikliği olduğunu bulduk, ancak AA hastaları ve sağlıklı kontroller arasında serum D vitamini düzeyleri açısından istatistiksel olarak anlamlı bir fark yoktu. 25 (OH) D eksikliği ile AA arasındaki ilişkiyi açıklığa kavuşturmak için daha fazla çalışmaya ihtiyaç vardır. Bize göre, AA hastalarında kan D vitamini seviyelerinin taranmasını ve eksik olması durumunda AA tedavi protokolüne oral D vitamini eklenmesini öneriyoruz.

Maddi Destek ve Çıkar İlişkisi

Bu yayın için herhangi bir maddi destek alınmamıştır.Yazarların herhangi bir çıkar dayalı ilişkisi yoktur.

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Turkish Journal of Clinics and Laboratory

To cite this article: Haberal B, Simsek EK. Tibiocalcaneal arthrodesis for the treatment of advanced stage Charcot arthropathy: Clinical and radiological outcome analysis of patients with diabetes mellitus followed for at least 2 years. Turk J Clin Lab 2020; 4: 225-231.

Original Article

Tibiocalcaneal arthrodesis for the treatment of advanced stage Charcot arthropathy: Clinical and radiological outcome analysis of patients with diabetes mellitus followed for at least 2 years

İleri evre Charcot artropatisinin tedavisi için tibiokalkaneal artrodez: Diyabetes mellituslu hastaların en az 2 yıllık takibi ile klinik ve radyolojik sonuç analizi

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Abstract

Aim: Charcot arthropathy (CA) described by Jean-Martin Charcot is a noninfectious degenerative and destructive process of the bones, joints and soft tissues in the area of the foot and ankle which associated with peripheral neuropathy. The purpose of this study was to evaluate the outcomes of tibiocalcaneal fusion using a retrograde hind foot ankle nail fixation system in 5 Charcot patients.

Material and Methods: Between 2014 and 2016, a total of 5 patients (4 women and 1 man) who underwent tibiocalcaneal arthrodesis for the treatment of advanced CA (Brodsky type 4) were evaluated. The demographic characteristics, clinical (AOFAS scores, early and late complications) and radiological (time for a union) evaluation parameters and patient satisfaction were analyzed before and after surgery.

Results: The mean preoperative AOFAS score was 64.8 ± 8.55 and mean postoperative score was 82.6 ± 12.99. The difference between preoperative AOFAS and postoperative AOFAS scores were statistically significant. During the clinical and radiological follow-up; infection, implant failure, and peri-implant fractures were checked and complications were recorded.

Conclusion: AOFAS scores were recorded before surgery after full weight bearing and it was found that talocalcaneal arthrodesis which was achieved with intramedullary nailing significantly increased AOFAS score compared to the preoperative AOFAS score.

Keywords: Charcot arthropathy; tibiocalcaneal arthrodesis; limb-salvage; nail fixation; diabetes mellitus

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Recevied: 02.06.2020 accepted: 16.07.2020
Doi: 10.18663/tjcl.770461

Öz

Amaç: Jean-Martin Charcot tarafından tanımlanan Charcotartropatisi, periferiknöropati ile ilişkili ayak ve ayak bileği bölgesindeki kemiklerin, eklemlerin ve yumuşak dokuların enfeksiyöz olmayan dejeneratif bir hastalığıdır. Bu çalışmanın amacı, 5 Charcotartropati hastasında retrograd arka ayak bileği fiksasyon sistemi kullanılarak yapılan tibiokalkaneal füzyonun sonuçlarını değerlendirmektir.

Gereç ve Yöntemler: 2014-2016 yılları arasında ileri Charcotartropati tedavisi için tibiokalkanealartrodez uygulanan 5 hasta (4 kadın ve 1 erkek) değerlendirildi. Ameliyat öncesi ve sonrası demografik özellikler, klinik (AOFAS skorları, erken ve geç komplikasyonlar) ve radyolojik (birleşme zamanı) değerlendirme parametreleri ve hasta memnuniyeti analiz edildi.

Bulgular: Ameliyat öncesi ortalama AOFAS skoru 64.8 ± 8.55 ve ortalama ameliyat sonrası skor 82.6 ± 12.99 idi. Ameliyat öncesi AOFAS ve ameliyat sonrası AOFAS skorları arasındaki fark istatistiksel olarak anlamlı bulundu. Klinik ve radyolojik takip sırasında; enfeksiyon, implant yetmezliği ve implant çevresi kırıklar ve komplikasyonlar kaydedildi.

Sonuç: AOFAS skorları ameliyat öncesi kaydedilmiş ve intramedüller çivileme ile elde edilen talokalkanealartrodezin AOFAS skorunu preoperatif AOFAS skoruna göre anlamlı derecede artırdığı bulunmuştur.

Anahtar kelimeler: Charcot artropati; tibiokalkaneal artrodez; uzuv kurtarma; çivileme; diabetes mellitus

Introduction

Charcot arthropathy (CA) described by Jean-Martin Charcot is a noninfectious degenerative and destructive process of the bones, joints and soft tissues in the area of the foot and ankle which associated with peripheral neuropathy.[1] Estimated prevalence of CA is ranging from 0.08 % to 13%.[2] In Charcot foot, osteolysis and demineralization occurs in bones as a result of microvascular dilatation and arterio-venous shunts associated with autonomous neuropathy and extremities are exposed recurrent micro traumas due to loss of sensation as a result of neuropathy. As a result of continuing ambulation on the insensitive extremities, capsular and ligamentous injuries, fractures and joint dislocations arises on foot.[3] In literature, numerous classification systems (called Eichenholz, Broadsky, Sanders and Frykberg, Rogers Classification.) are described for the Charcot foot according to severity, localization and complexity of the disease (Figure 1)(Table 1).[4]

With the increasing prevalence of diabetes mellitus (DM) worldwide, treatment of Charcot arthropathy and its potentially limb-threatening complications in the foot and ankle is gaining importance. Treatment options include nonoperative therapies (offloading, cast applications, medical management) and surgical treatments. The goal of treatment, whether operative or nonoperative, is to achieve a plantigrade foot with osseous stability.[5] If the efforts for nonoperative treatment of unbraceble or unstable foot fails, below the knee amputation is then required. To provide limb-salvage surgery few options are available. Current surgical options to stabilize limb include pan-talar, tibiotalocalcaneal or talocalcaneal arthrodesis. Pantalar or tibiotalocalcaneal arthrodesis may not be possible in the presence of associated talar avascular necrosis, fragmentation or resorption. There is a small number of reports in the literature about tibiocalcaneal arthrodesis.[6]

The purpose of this study was to evaluate the outcomes of tibiocalcaneal fusion using a retrograde hind foot ankle nail fixation system in 5 Charcot patients with severe ankle and hindfoot deformity and total talar bone loss.

Material and Methods

Patients

Between 2014 and 2016, a total of 5 patients (4 women and 1 man) who underwent tibiocalcaneal arthrodesis for the treatment of advanced CA (Brodsky type 4) were evaluated (Figure 2,3,4,5,6). Patients who were diagnosed with Charcot-associated ankle and hindfoot deformity but had not yet developed deep (exposed deep fascia) foot or ankle ulceration, were considered candidates for tibiocalcaneal arthrodesis and included in the study cohort. The degree of ankle and hind foot instability and deformity had to be Advanced enough and associated with real or potential cutaneous compromise to be considered for tibiocalcaneal arthrodesis. Exclusion criteria included a diagnosis of ulceration deep to the deep fascia, osteomyelitis and/or peripheral arterial

disease (PAD) not amenable to revascularization. All the patients had insulin dependent type II DM at the time of surgery and having previously been given a recommendation of a below-knee amputation.

For all patients, nails were applied by the same surgeon with a retrograde approach (RCA). The institutional review board approval (KA 20/16) was obtained. The principles outlined in the Declaration of Helsinki were followed and written informed consent from all participants was obtained.

Scales

- Brodsky's classification: This classification is an anatomic-based classification system for Charcot arthropathy. It is specific to the foot and based on the most common regions affected(Table 1, Figure 1).[7]

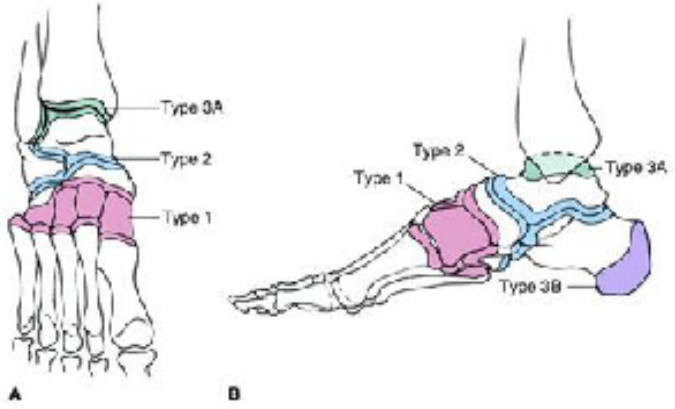

Figure 1: AP (A) and lateral (B) drawings demostrating Brodsky's anatomic classification of the Charcot foot.

Table 1: Descriptive table of the Brodsky Classification

Brodsky Classification	
Type 1	Involves tarsometatarsal and naviculocuneiform joints
Type 2	Involves subtalar, talonavicular or calcaneocuboid joints
Type 3A	Involves tibiotalar joint
Type 3B	Follows fracture of calcaneal tuberosity
Type 4	Involves a combination of areas
Type 5	Occurs solely within forefoot

- The American Foot and Ankle Score (AOFAS):This Scale combines subjective scores of pain and function provided by the patient with objective scores based on the surgeon's physical examination of the patient.[8]

- Visual AnalogueScale (VAS): This Scale was accepted in the literature and in this study it was used to evaluate the patients' pain between 0 and 10 points. When the scale score increased, the patient's pain level was considered to increase.[9]

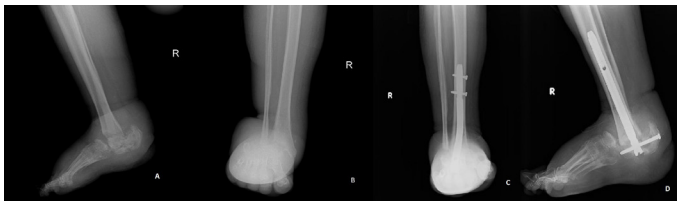

Figure 2: Pre-operative and post-operative plain radiographs of Patient 1.

A/B: Lateral and Anterior-Posterior plain radiograph of the ankle (pre-operative)

C/D: Anterior-Posterior and Lateral plain radiograph of the ankle (post-operative)

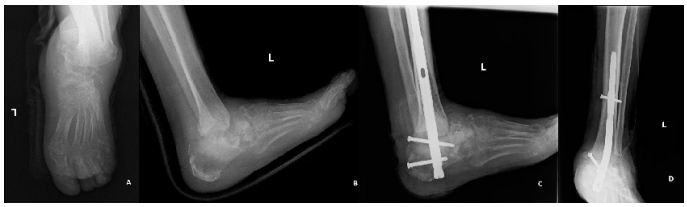

Figure 3: Pre-operative and post-operative plain radiographs of Patient 2.

A/B: Anterior-Posterior and Lateral plain radiograph of the ankle (pre-operative)

C/D: Lateral and Anterior-Posterior plain radiograph of the ankle (post-operative)

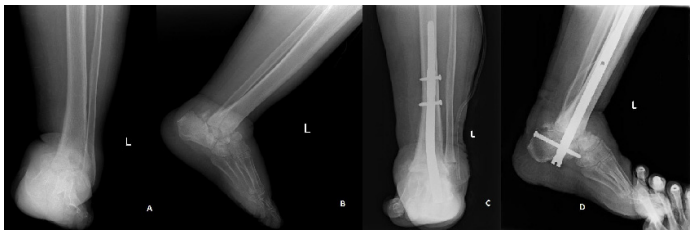

Figure 4: Pre-operative and post-operative plain radiographs of Patient 3.

A/B: Anterior-Posterior and Lateral plain radiograph of the ankle (pre-operative)

C/D: Anterior-Posterior and Lateral plain radiograph of the ankle (post-operative)

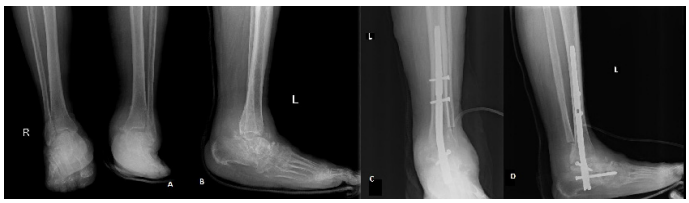

Figure 5: Pre-operative and post-operative plain radiographs of Patient 4.

A/B: Anterior-Posterior and Lateral plain radiograph of the ankle (pre-operative)

C/D: Anterior-Posterior and Lateral plain radiograph of the ankle (post-operative)

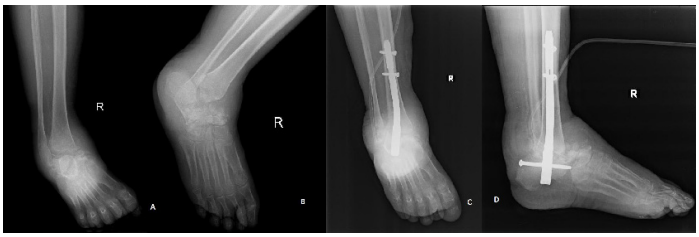

Figure 6: Pre-operative and post-operative plain radiographs of Patient 4.

A/B: Anterior-Posterior and Oblique plain radiograph of the ankle (pre-operative)

C/D: Anterior-Posterior and Lateral plain radiograph of the ankle (post-operative)

Surgical Technique

Patients were positioned supine on the standard operating table after sterilization and coverage performed. A lateral curvilinear skin incision to the ankle joint was made. Lateral malleolus osteotomy was performed then talar bone fragments were excised. All the fibrous tissue and inflamed synovial tissues were also debrided. The articular surface of the distal tibia and calcaneus were removed with a power saw perpendicular to the weight bearing axis of the tibia. Thought the created regular shaped surfaces, the positioning of the ankle at neutral dorsiflexion, neutral to 5 degrees of valgus and similar external rotation to the contralateral extremity was obtained. The nail entry point was similar to that described previously in the literature.[6,10] A guide wire was passed to the proximal tibia and the intramedullary canal was reamed. After nail length was determined, the nail (ExpertHAN, Depuy-Synthes) was placed in the proper position. Percutaneous distal locking of the nail was achieved using the insertion/aiming guide. Proximal locking was done with a freehand technique with image intensification monitoring. After compression of the arthrodesis site was achieved, distal fibula used as a bone graft.

A below-knee splint was used for 7-10 days then weight bearing total contact cast was applied, postoperatively. Clinical and radiological evaluations of the implant status and bone union were evaluated following each month. Presence of bony union at the arthrodesis site the cast was removed and the patient then allowed limited weight bearing with a walker for 4-6 weeks. At the end of the post-operative therapy, period patient was allowed to walk freely with protective shoes.

Statistical analysis

The demographic characteristics, clinical (AOFAS scores, early and late complications) and radiological (time for a union) evaluation parameters and patient satisfaction were analyzed before and after surgery. Union of the tibiocalcaneal fusion was determined both clinically and radiographically by the lead author. Mean values and Standard deviations was used for parametric data and median ± distribution width was used for nonparametric data. Data were analyzed by using SPSS (Statistical Package for the Social Sciences) for Windows v24.0.

Results

The mean patient age was 62.2±3.49 years and the mean body weight was 78.2 ± 13.24 kilograms (range to 68-101). All the patients had DM type 2 at the time of surgery and had a Brodsky Type 4 Charcot foot. The mean duration of DM was 12±4.85 years (range 7 to 19). Of the 5 patients (4 women, 1 man) in this study, 3 patients (3 women) had also chronic renal failure. All patients had a normal distal blood supply. Patients enrolled in the study were observed for a period of 34.8 ± 10.73 (range 24 to 48) months follow-up after free walking. (Table 2, Table 3)

Table 2: Descriptive table of all patients. (DM: diabetes mellitus, VAS: visual analog scale, AOFAS: The American Foot and Ankle Score)

	Patient number				
Variable	**1**	**2**	**3**	**4**	**5**
Age (year)	58	67	64	62	60
Gender	Female	Male	Female	Female	Female
Body weight (kg)	68	70	76	101	76
Duration of DM (month)	7	19	14	8	12
Creatinine	7.23	0.81	0.59	5.82	6.58
Brodsky's grade	4	4	4	4	4
Preoperative VAS	3	4	2	3	4
Preoperative AOFAS	76	54	64	60	70
Postoperative VAS	1	4	1	1	2
Postoperative AOFAS	95	62	92	80	84
Unsupported walking	Yes	No	Yes	Yes	Yes
Duration of union (week)	17	28	12	12	12
Osteomyelitis	No	Yes	No	No	No
Complication	No	Yes	No	No	No
Postoperative Foot Ulceration	-	-	-	-	-
Implant failure	-	-	-	-	-
Peri-implant fractures	-	-	-	-	-
Postoperative follow-up (month)	24	42	48	36	24

Table 3: Descriptive table of all patients (DM: diabetes mellitus, VAS: visual analog scale, AOFAS: The American Foot and Ankle Score)

Variable	Minimum	Maximum	Mean/ Median	SD
Age	58	67	62.20*	3.49
Body weight (kilogram)	68	101	78.20*	13.24
Duration of DM (month)	7	19	12*	4,85
Creatinine	0.59	7.23	4.21*	3.24
Preoperative VAS	2	4	3	0.84
Preoperative AOFAS	54	76	64.80*	8.55
Postoperative VAS	1	4	1	1.30
Postoperative AOFAS	62	95	82.60*	12.99
Unsupported walking	1	2	2	0.45
Duration of union (week)	12	28	12	6.94
Osteomyelitis	0	1	0	0.45
Complication	0	1	0	0.45
Postoperative follow-up (month)	24	48	34.80*	10.73

(*) Mean value

The results of clinical and radiological observation are summarized in Table 3. The mean preoperative AOFAS score was 64.8 ± 8.55 and mean postoperative score was 82.6 ± 12.99. The American Foot and Ankle Score values increased postoperatively, but the Visual Analog Scale (VAS) scores did not change among the patients. The preoperative and postoperative VAS values were not different among the patients (Table 4). All patients except one patient (patient 3) could walk without support and all of the patients had painless foot and no ulcerative wound on the soles. Union was achieved in all patients in an average of 12 ± 6.94 weeks (range 12-28). During the clinical and radiological follow-up; infection, implant failure, and peri-implant fractures were checked and only "patient 2" had osteomyelitis. Patient satisfaction was excellent in 4 patients and fair in 1 patient.

Table 4: The preoperative and postoperative comparison of AOFAS and VAS scores

Variable (I/J)	t/ Z	p
Preoperative AOFAS/ Postoperative AOFAS	-8.575*	0.006
Preoperative VAS/ Postoperative VAS	-1.890	0.059

The Paired Samples t test and Wilcoxon Signed Ranks test, p<0.05 (AOFAS : The American Foot and Ankle Score, VAS: Visual Analog Scale, t: t score, Z: Z score) (*) *t* value

Discussion

In the last phase (called Broadsky type 4) of the Charcot arthropathy, surgical options are limited and like an amputation generally limb threatening. The deformity can lead to ankle instability and skin ulcers which can result in osteomyelitis with the associated risk of possible limb amputation. With the addition of total talar bone loss to the disease, the situation becomes more difficult and complicated. Schneekloth et al. systematically reviewed surgical treatment options in diabetic patients with Charcot neuropathy in the literature and 77 of the 860 cases (%8.9) were amputated.[11] However, in current literature, there has been increasing interest in surgery to avoid amputations and provide the plantigrade foot with osseous stability. Schneekloth et al. show that the most common surgical procedure is tibiotalocalcaneal arthrodesis (%19.8 of all cases) and limb salvage procedures at the end stage Charcot foot gains popularity but no information has been given about the cases of talocalcaneal arthrodesis in their studies.[11] This may be due to the fact that Charcot arthropathies with total talar bone loss are rare cases which are published in the literature as case reports or case series. Different surgical fixation techniques are used for patients with Charcot arthropathy to achieve talocalcaneal arthrodesis in the literature and the most applied technique is intramedullary nailing. Talectomy with talocalcaneal fusion using retrograde intramedullary nailing is a good salvage option for patients with Charcot arthropathy. In tibiocalcaneal fusion, it is important to achieve rigid fixation and a plantigrade foot.[12,13] In patients with Charcot arthropathy, obtaining a plantigrade and non-ulcerative foot that patients can step on without using a supportive device is one of the most important goals of the treatment table (Figure 7). However, the nail design used in this study (ExpertHAN, Depuy-Synthes) is for patients who have talus. Therefore, in patients who undergo tibiocalcaneal arthrodesis, the configuration of the screws applied through the nail may be inadequate. This can be considered in the design of new nails for ankle arthrodesis. In present study, there was no stability problem consistent with other studies using intramedullary nails, and no additional fixation method was needed to contribute to stability. As demonstrated by Caravaggi et al. it is possible to achieve this with intramedullary nails and consistent with them our study showed that all patients could walk freely using the only custom-made shoes.[14] Furthermore, study findings demonstrated that nail arthrodesis achieved total bone fusion rate and there was no need for bone grafts except distal fibula. In contrast to Abhijit et al. the average duration of a bone union in this study was shorter.[15] Good results have also been reported in patients with plate-screw fixation.[15-17] All patients had a stable, plantigrade foot and were pleased with the outcome.

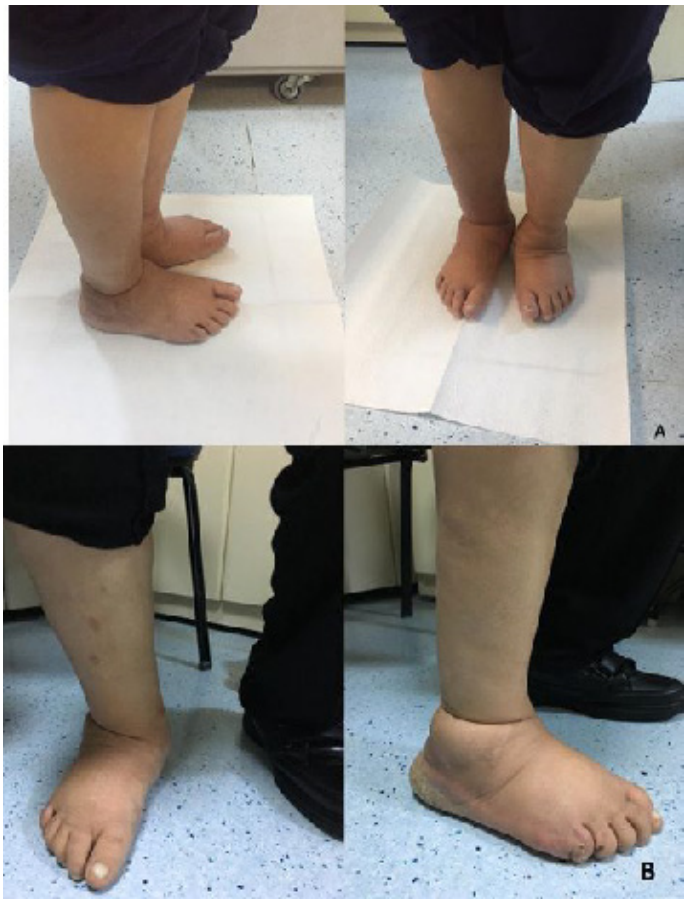

Figure 7: Post-operative photographs of the patients (Published with permission from patients).

A: Patient 3 (Post-operative 6th month)

B: Patient 5 (Post-operative 12th month)

On the other hand, when studies with patients undergoing talocalcaneal arthrodesis are examined in literature, no objective scoring system used to assess functional and clinical outcomes after surgery except Abhijit et al or no statistical analysis of whether the relationship between the parameters and results are meaningful was found.[6, 13, 15-18] In present study, AOFAS scores were recorded before surgery after full weight bearing and it was found that talocalcaneal arthrodesis which was achieved with intramedullary nailing significantly increased AOFAS score compared to the preoperative AOFAS score. Additionally, no statistical relationship was observed among the DM duration, chronic renal disease and bone union time. Furthermore, probability of the unsupported walking score of the patients could be increase if this postoperative AOFAS scores would be increased. In accordance with this data, patient satisfaction was recorded excellent in 4 patients and good in 1 patient. In the studies, which include patients who had Charcot arthropathy with total talar bone loss and treated with intramedullary nailing, the most common complication is soft tissue infection. Other common complications are amputations, stress fractures, and implant failures. In our study, osteomyelitis was observed in one patient. This may be due to a limited number of patients. On the other hand, correlation analysis results showed that osteomyelitis or other complication related to the surgery could decrease the unsupported walking score of the patients, postoperatively.

The present study had some limitations. Firstly, the number of the patients included in this study was small. Therefore, power-analysis could not be performed. Secondly, the outcome of the surgical treatment was evaluated retrospectively and the postoperative follow-up period was inconsistent and ranged from 24 to 48 months. Thirdly, considering polyneuropathy associated reduction of the sensation of pain, the results of the AOFAS scores must be viewed carefully.

Conclusion

The recent increase in the number of patients with diabetes has increased the frequency of Charcot's ankle also. The deformity can lead to ankle instability and skin ulcers which can result in osteomyelitis with the associated risk of possible limb amputation. Limb salvage is an important alternative treatment modality instead of transtibial amputation. Talectomy with talocalcaneal fusion using retrograde intramedullary nailing is a good salvage option for patients with Charcot arthropathy. In tibiocalcaneal fusion, it is important to achieve rigid fixation and a plantigrade foot. Patients with a stable and plantigrade foot will be satisfied with the results.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Turkish Journal of Clinics and Laboratory

To cite this article: Esmer AC, Mansiroglu CK, Akan A, Tazeoglu D. Factors increasing surgery success in primary hyperparathyroidism. Turk J Clin Lab 2020; 4: 232-236.

Original Article

Factors increasing surgery success in primary hyperparathyroidism

Primer hiperparatiroidizm cerrahisinde başarıyı artıran faktörler

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Abstract

Aim: Standart procedure for primary hyperparathyroidism patients' is two sides neck exploration, during the last years minimal incision started to be used for primary hyperparathyroidisim patients at primary hyperparathyrodism patients. Some researchers had been done to which patients should perform minimal incision surgery that a set of indexes proposed to use. So we can try to show which parameters should be use for get better surgery results.

Material and Methods: Files of the patients, that undergo surgery for primary parathyroidism between January 2009-2016, will be studied retrospectively.

Results: There 166 patients operated for primary hyperparathyroidism. Fourteen of these patients have multiple gland disease. There is no difference for single gland disease and multigland disease patients between age and gender statistically. Multiple glands disease patients' pathology specimens lenght and weight is lower than single gland disease group statistically. Preoperative and postoperative parathormone (Pth) and calcium levels have no statistical difference. Comparing minimal invasive parathyroidectomy (MIP) and bilateral neck exploration parathyroidectomy shows there is no statistically difference between them. Avaible parameters applied advised parameters.

Conclusion: There is scoring systems, that made from combination of biochemical parameters and screening methods, seperate single gland disease and multiple gland disease. We evaluated these scoring system among our patients. CaPTHUS scoring system seems useful at our patient group. Wisconsin index is statisticaly meaningless with slight difference. So there is need to more crowded and prospective studies to be done for seperating multi gland disease and solitary adenoma. Comparing Minimal invasive parathyroidectomy and bilateral neck exploration parathyroidectomy shows that MIP is a safe procedure in selected patients.

Keywords: Primary hyperparathyroidism; single gland disease; multigland disease; minimal invasive parathyroidectomy

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Recevied: 06.11.2019 accepted: 10.05.2020
Doi: 10.18663/tjcl.641304
*Text presented as poster at "8. Ulusal Endokrin Cerrahi Kongresi" on 27-30 April 2017,Antalya

Öz

Amaç: Primer hiperparatiroidizm hastalarında son yıllarda standart bilateral boyun eksplorasyonu yerine, seçilmiş hastalarda minimal insizyon ile paratiroidektomi tercih edilmeye başlanmıştır. Hangi grup hastaya minimal insizyonun uygun olduğunu tespit etmek için bazı çalışmalar yapılmış ve bunlara dayanarak bir takım indeksler önerilmiştir. Biz de bu çalışmada kendi klinik olgularımızda bu parametrelerin geçerliliğini değerlendirmek amacıyla bu çalışmayı planladık.

Gereç ve Yöntemler: Çalışmamızda Ocak 2009 ve Ocak 2016 tarihleri arasında Okmeydanı Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniğinde Primer hiperparatiroidizm tanısıyla ameliyat edilmiş hastaların dosyaları retrospektif olarak incelenip sonuçlar istatistiksel olarak değerlendirildi.

Bulgular: Primer hiperparatiroidi tanısı ile ameliyat olan 166 hasta çalışmaya alındı. Bu hastaların 14'ünde çoklu bez hastalığı olduğu görüldü. Tekli bez ile çoklu bez hastaları arasında yaş ve cinsiyet açısından istatistiksel olarak fark olmadığı saptandı. Çoklu bez hastalarında piyes boyutu ve ağırlığının istatistiksel olarak daha düşük olduğu gözlendi. Ameliyat öncesi ve sonrası kalsiyum ile parathormon (Pth) değerlerinde ise bir fark olmadığı gözlendi. Minimal invazif paratiroidektomi (MIP) ya da bilateral boyun eksplorasyonu ile paratiroidektomi yapılan hastalar istatistiksel olarak karşılaştırılarak gruplar arası fark olmadığı gözlendi. Mevcut parametreler önerilen indekslere uygulandı.

Sonuç: Primer hiperparatiroidizm hastalarında tekli bez ve çoklu bez hastalığı ayrımı için biyokimyasal parametreler ile görüntüleme yöntemlerinin korelasyonuna dayalı skorlama sistemleri öneren çalışmalar mevcuttur. Bu skorlama sistemlerinin ve değerlendirme parametrelerinin etkinliği bizim hastalarımızda değerlendirildi. Bizim hastalarımızda CaPTHUS skorlama sisteminin faydalı olduğu tespit edilirken, Wisconsin indeksi ise hasta sayısının azlığından dolayı istatistiksel olarak az bir farkla anlamlandırılamamıştır. Bu yüzden tekli bez ve çoklu bez hastalığı ayrımını kolaylaştırmak için daha geniş ve prospektif çalışmaların gerekliliği söz konusudur. Minimal insizyon ile bilateral boyun eksplorasyonu karşılaştırmasında, seçilmiş hastalarda MIP için güvenilir olduğu belirlenmiştir.

Anahtar kelimeler: Primer hiperparatirodizm; tekli bez hastalığı; çoklu bez hastalığı; minimal invazif paratiroidektomi

Introduction

Primary hyperparathyroidism is most common reason of hypercalcemia for hospital applications. Primary hyperparathyroidism is a clinical condition caused by excessive parathyroid hormone (PTH) synthesis from parathyroid glands [1]. It occurs one in every 500 women and one in 2000 men after 4th decades of life. It is four fold more common in women than in men.

Standard treatment for primary hyperparathyroidism is bilateral neck exploration. First successful parathyroidectomy with bilateral neck exploration was performed in 1925 by Felix Mandl in a patient with primary hyperparathyroidism with osteitis fibrosa cystica in Vienna [2]. Devoloping new imaging techniques make it possible to perform parathyroidectomy with minimally invasive surgical techniques. Unilateral neck exploration is first performed by Jeffrey Stevens at patients with single parathyroid gland disease in 1979 [3]. Minimally invasive parathyroidectomy facilitated by intraoperative nuclear mapping was first described by James Norman and Hemant Chheda in 1997 [4].

Kebebew et al. formed CaPTHUS scoring system which could be used to differentiate between single and multiple gland disease based on blood values, ultrasonography (USG) and methoxyisobutyl isonitrile (MIBI) scintigraphy results in 2006 [5]. In 2013, Mazeh et al. demonstrated that the Wisconsin index obtained from the multiplication of PTH and calcium values could distinguish between single and multiple gland disease and thus could focus on minimally invasive surgery [6].

In our study, we aimed to determine the convenient surgical treatment in patients with primary hyperparathyroidism by detecting single or multipl gland disease cases accompanied by biochemical parameters and radiological imaging. Thus, performing focused surgery can reduce complications and the risk of re-surgery compared to the exploration of all glands.

Material and Methods

In our study, we searched retrospectively the files of the patients who underwent surgery for primary parathyroidism between January 2009 – January 2016 in Okmeydanı Training and Research Hospital Department of General Surgery.

The study was approved by The Ethic Committee of Okmeydanı Training and Research Hospital (28/6/2016–504). Informed

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consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

The inclusion criterias of the study were diagnosis of adenoma as histopathologically, postoperative PTH values decreased more than 50% and normal serum calcium levels of postoperatively 6 months follow-up. The exclusion criterias of the study were patients without postoperative follow-up and diagnosis of adenocarcinoma by histopathology.

Patients were evaluated with age, sex, serum calcium levels, PTH, USG and MIBI scintigraphy, tumor localization, size and weight of pathological specimen. We used Wisconsin index for evalution, Wisconsin index based on multiplication of PTH and calcium level.

We applied CaPTHUS scoring system based on PTH, serum calcium level, USG and MIBI scintigraphy. In this scoring system; serum calcium values higher than 12 mg/dl, PTH more than 2 fold higher than normal, one gland involvement in MIBI, one gland involvement in USG and the correlation between USG and MIBI findings was scored by one point. In this scoring system based on a score of 5, low sensitivity (44%), high specificity (100%) and high positive predictive value (100%) were detected in detecting single gland disease in patients who scored 3 or more.

We included 166 patients for study. 152 of them were single gland disease, and 14 patients were multiple gland disease. Statistical analysis was conducted by SPSS 15.0 and $p>0.05$ was accepted for statistically significant difference.

Results

One hundred sixty six patients were operated due to primary hyperparathyroidism. One hundred thirty one of these patients were female (78.9%), and 35 were male (21.1%). The mean age was 56.5 years (20-85). The mean age of the female population was 56.6 years, and the male population was 56.1 years.

The mean preoperative calcium level of the patients was 11.25 mg dl (8.3-14.9). The mean preoperative PTH value of the patients was 360.5 pg/ml (31-2479). The mean Wisconsin index that was 3606.

The mean weight of parathyroid gland was 1567 mg (110-13270 mg). The mean length of pathological specimen's longest axis was 20.8 mm (6-50).

The patients were divided into two groups, which single gland disease as "Group 1" and multiple gland disease as "Group 2". One hundred and fifty two (91.5%) patients were single gland disease, and 14 (8.5%) were multiple gland disease. 6 patients of multiple gland disease had 2 glands, and 8 patients had 4 gland hyperplasia. In Group 1, there were 124 female and 28 male patients with a mean age of 56.8 years. In Group 2, 10 female and 4 male patients with a mean age of 56.3 years. There is no statiscally significance at age and sex distrubition between two groups (Student T Test $p=0.95$, Mann Whitney U $p=0.37$).

The mean preoperative serum calcium level was 11.2 mg/dl and the mean PTH level was 326.8 pg/ml in Group 1. The mean serum calcium level of first postoperative day was 9.3 mg/dl and PTH level was 58.0 pg/ml (Table 1).

The mean preoperative serum calcium level was 11.1 mg/dl and PTH level was 188.1 pg/ml in Group 2. The mean serum calcium level of first postoperative day was 9.7 mg/dl and PTH was 38.3 pg/ml (Table 1).

Table 1: Comparison of age, preoperative serum calcium level, PTH level and weight of the groups

		Age (year)	Pre Ca (mg/dl)	Pre PTH (pg/ml)	Weight (mg)
Single Gland	N	152	152	152	152
(Group 1)	Mean	56.8	11.2	11.2	1686.5
	Standard Deviation	14.38	.87	389.8	1941.7
	Minimum	20	8.3	31.0	110
	Maximum	85	13.8	2479	13270
Multiple Gland	N	14	14	14	14
(Group 2)	Mean	56.3	11.1	188.1	726.4
	Standard Deviation	17.1	.80	147.0	556.1
	Minimum	20	9.9	47.0	240
	Maximum	84	12.7	473.4	2400

The mean weight of parathyroid gland was 1686.5 mg in Group 1 and 726.4 mg in Group 2. The mean size of the longest axis of pathological specimen was 21.2 mm in Group 1 and 15.8 mm in Group 2 (Table 2).

Table 2: Comparison of postoperative serum calcium level, PTH level, Wisconsin index and specimen size of the groups

		Post Ca (mg/dl)	Wiscon-sin index	Length (mm)	Post PTH (pg/dl)
Single Gland	N	152	152	152	152
(Grup 1)	Mean	9.3	3739.3	21.2	58.0
	Standard Deviation	1.0	4473.7	11.0	112.6
	Minimum	6.8	316.2	6	1.8
	Maximum	14.7	26525.3	100	1155.1
Multiple Gland	N	14	14	14	14
(Grup 2)	Mean	9.7	2165.6	15.8	38.38
	Standard Deviation	1.1	1782.8	5.8	72.3
	Minimum	8.0	512.3	10	5.1
	Maximum	12.8	5633.4	32	284.7

The mean Wisconsin index was 3739.3 in Group 1 and 2165.6 in Group 2 (Table 2). There is no statistically significance between the Wisconsin index among the groups (Mann Whitney U test p=0.06).

There is no statistically significance of preoperative serum calcium levels between groups (Mann Whitney U test p=0.51). There is no statistically significance of postoperative calcium levels between the groups (Mann Whitney U test p=0.21). There is statistically significance between the groups for preoperative PTH value (Mann Whitney U test p=0.05). There is statistically significance between the groups for postoperative PTH values (Mann Whitney U test p=0.01) (Table 3).

Table 3: Comparison of PTH level and serum calcium level of groups

	Group 1		Group 2		P value
	Mean	SD	Mean	SD	
Preop Calcium (mg/dl)	11.2	0.87	11.1	0.80	0.51
Postop Calcium (mg/dl)	9.3	1.00	9.7	1.19	0.21
Preop PTH (pg/dl)	326.8	389.86	188.1	147.05	0.05
Postop PTH (pg/dl)	58.0	112.69	38.3	72.32	0.01

The size of the specimens was found statisticaly significant in Group 1 (Mann Whitney U p=0.03). The mean weight of the specimens was found statisticaly significant in Group 1 (Mann Whitney U test p=0.002) (Table 4).

Table 4: Comparison of size and weight of specimen between groups

	Group 1		Group 2		P Value
	Mean	SD	Mean	SD	
Specimen Length (mm)	21.2	11.05	15.8	5.82	0.03
Specimen Weight (mg)	1686.5	1941.73	726.4	556.13	0.002

We used CaPTHUS for 78 of 166 patients, because of both USG and MIBI scintigraphy were only used in these 78 patients. Five of these 78 patients had multiple gland disease. CaPTHUS score of single gland disease was 0 in 5 patients, 1 in 21 patients, 2 in 15 patients, 3 in 17 patients, 4 in 12 patients and 5 in 3 patients. CaPTHUS score of multiple gland disease was 0 in 2 patients, 1 in 2 patients, 2 in 1 patient. (Figure 1).

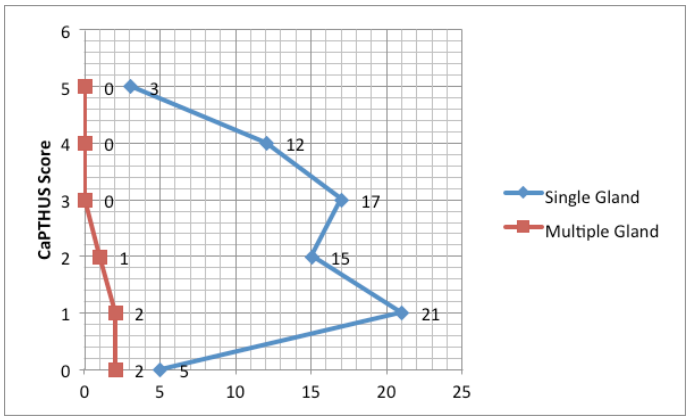

Figure 1. Distribution of the CaPTHUS Score Between Single and Multiple Gland Disease

Discussion

Primary hyperparathyroidism is a disorder caused by one or more parathyroid glands' excessive PTH synthesis [7]. Surgical treatment is essential in the treatment of primary hyperparathyroidism. The success rates of surgical treatment are 94% for the first approach and 86% for the second approach [8].

The procedure of parathyroid surgery for the treatment of parathyroid adenoma is controversial. More than %80 of primary hyperparathyroidisim is related to parathyroid adenomas. Surgical removal of the gland is preferred for treatment of adenomas [9]. Misdiagnosis of single or multiple gland disease is one of the factor that decrease the success in parathyroid adenoma surgery.

Mazeh et al.'s study on primary hyperparathyroidism, 1235 patients were examined; single gland disease was detected in 1000 patients and multiple gland disease was detected in 235 patients [6]. They formulized Wisconsin index based on multiplication of PTH and serum calcium level. Wisconsin index is significantly lower in the group of multiple gland disease (Chi Square p<0.001). We found a slightly difference with no statistical significance in Wisconsin index between the groups (p=0.06). We think this result is due to low case number.

The size of the specimen that evaluated by measuring the longest axis was found significantly lower in the multiple gland disease group. Gland weight was statistically significantly lower in the multiple gland disease group. We can use this information for determination of single gland disease by a cut-off value in the size and weight of specimen. Thus, it can show us the success of exploration while the surgery.

Kebebew et al. searched the files of 238 patients retrospectively who underwent parathyroidectomy. Single gland disease was detected in 179 patients and multiple gland disease was detected in 59 patients [5]. They developed a scoring system named CaPTHUS. Seventy eight of 166 patients in our study

had USG and also MIBI scintigraphy, and these patients were evaluated according to CaPTHUS scoring system. Five of these 78 patients had multiple gland disease. Like Kelebew et al. study none of multiple gland patients score 3 or more. Two of multiple gland disease patients score was 0, two patients scored 1 and one patient scored 2. All of these 5 patients MIBI scintigraphy and USG screening results were negative. Most experienced surgeons evaluate the patients without both of USG and MIBI scintigraphy and this is the limitation of CaPTHUS. USG and MIBI scintigraphy were found effective as imaging methods in the determination of adenoma localization and were recommended by the authors as the first screening test [10].

Parathyroid adenomas develop more frequently in lower parathyroid gland [11-13]. In our study adenomas localized upper left in 16 (%10.5) patients, upper right in 18 patients (%11,8), lower left in 68 (%44.7) patients and lower right in 50 (%32.9) patients. It was found compatible with literature [14,15].

Conclusion

The main goal of primary hyperparathyroidism surgery is to distinguish single and multiple gland disease. In this regard, scoring systems based on biochemical parameters, gland size, weight and correlation of imaging methods have been designed. CaPTHUS is one of these scoring systems and found beneficial for our study. In our study, Wisconsin index is not statistically significant due to the insufficient number of patients. During neck exploration removal of adenoma over the cut-off values can refer to adequate surgery, and it could avoid complications due to unnecessary exploration. We can prefer minimally invasive parathyroidectomy for patients which have CaPTHUS score 3 or more. Minimally invasive parathyroidectomy can reduce complications like hypoparathyroidism and vocal cord paralysis. Therefore, operating room efficiency is increased by reducing surgery time.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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To cite this article: Kurtul A, Gok M, Ornek E. The relationship between serum vitamin d and bare-metal in-stent restenosis in patients with stable coronary artery disease. Turk J Clin Lab 2020; 4: 237-242.

Original Article

The relationship between serum vitamin d and bare-metal in-stent restenosis in patients with stable coronary artery disease

Stabil koroner arter hastalığı olan hastalarda serum d vitamini ve çıplak metal stent restenozu arasındaki ilişki

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Abstract

Aim: It has been shown that low levels of vitamin D are associated with increased cardiovascular risk factors and adverse events. The relationship between serum vitamin D level and bare-metal stent in-stent restenosis was investigated in our study.

Material and Methods: A total of 181 patients with stable coronary artery disease and previously implanted (>3 months) bare-metal stent were included in the study. Two groups were formed according to angiographic results as Group 1 (≥50% in-stent stenosis) and Group 2 (<50% in-stent stenosis). Serum vitamin D measurements were performed by reverse-phase HPLC.

Results: The mean serum vitamin D levels were found to be significantly lower in Group 1 compared to Group 2 (17.7 ± 5.3 ng/ml and 20.9 ± 6.7 ng/ml, p<0.01, respectively) and length of stent was longer in Group 1 compared to Group 2 (18.7 ± 5.3 mm and 17.1 ± 11.2 mm, p<0.01, respectively). In multivariate logistic regression analysis, only low level of serum vitamin D and stent length were independent risk factors for bare-metal in-stent stenosis.

Conclusion: Low level of vitamin D might be related to fibrosis and inflammation resulting in in-stent stenosis. Further studies are warranted to determine whether vitamin D supplementation could prevent progression of stent re-stenosis.

Keywords: coronary artery disease; in-stent stenosis; serum 25(OH)D3

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Recevied: 25.09.2019 accepted: 08.01.2020
Doi: 10.18663/tjcl.624722

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Öz

Amaç: Düşük D vitamini düzeylerinin artmış kardiyovasküler risk faktörleri ve yan etkiler ile ilişkili olduğu gösterilmiştir. Çalışmamızda serum D vitamini düzeyi ile çıplak metal stent restenozu arasındaki ilişki araştırıldı.

Gereç ve Yöntemler: Çalışmaya stabil koroner arter hastalığı olan ve daha önce çıplak metal sten implante edilmiş (> 3 ay) olan toplam 181 hasta dahil edildi. Anjiyografik sonuçlara göre Grup 1 (≥% 50 stent darlığı) ve Grup 2 (<% 50 stent darlığı) olarak iki grup oluşturuldu. Serum D vitamini ölçümleri ters faz HPLC ile yapıldı.

Bulgular: Ortalama serum D vitamini düzeyleri Grup 1'de Grup 2'ye göre anlamlı derecede düşük bulundu (sırasıyla 17.7 ± 5.3 ng / ml ve 20.9 ± 6.7 ng / ml, p <0.001) ve stent uzunluğu Grup 1'de Grup 2'ye göre daha uzun bulundu (sırasıyla 18.7 ± 5.3 mm ve 17.1 ± 11.2 mm, p <0.001). Çok değişkenli lojistik regresyon analizinde, sadece düşük serum D vitamini düzeyi ve stent uzunluğu, çıplak metal stent restenozu için bağımsız risk faktörleriydi.

Sonuç: Düşük D vitamini düzeyi stent stentenozuna neden olan fibrozis ve inflamasyonla ilişkili olabilir. D vitamini takviyesinin stent restenozunu önleyip önleyemeyeceğini belirlemek için ileri çalışmalar yapılması önerilir.

Anahtar kelimeler: koroner arter hastalığı; stent restenozu; serum 25(OH)D3

Introduction

Serum 25-hydroxyvitamin D [25(OH)D3] is the main circulating form of vitamin D (Vit D). In cross-sectional and observational studies, it has been shown that low levels of 25(OH) D3 are associated with increased prevalence of cardiovascular disease (CVD) and risk factors.[1-5] Vitamin D deficiency is recently recognized as an independent risk predictor for CVD. [1-5] The pathobiologic mechanisms related these effects are unclear, however a possible mechanism may be linked to vitamin D regulation of related fibrotic pathways.[6]

Although drug-eluting stents (DES) are increasingly used for their much lower in-stent stenosis rate compared to balloon angioplasty, widespread use of bare metal stents (BMS) are currently going on, especially in developing countries. Bare metal stent successfully prevents abrupt closure of the artery and reduces the restenosis rate. The efficacy of BMS implantation was hugely hampered by vascular smooth muscle cell proliferation and the resultant neointimal hyperplasia, which is the main mechanism responsible for restenosis.[7]

The aim of the current study was to determine the relationship between serum vitamin D level and coronary bare-metal in-stent restenosis in patients with stable coronary artery disease (SCAD).

Material and Methods

A total of 243 consecutive patients with previously stented were reviewed for possible contribution to the study. Diagnostic coronary angiography was performed to all patients due to anginal complaints and/or abnormal exercise/pharmacological stress tests. However after performing below mentioned exclusion criteria, we enrolled a total of 181 patients with BMS. Two groups were performed according to angiographic results that 106 patients having in-stent stenosis of at least 50% formed Group 1 and the remaining 75 patients without stenosis or with <50% stenosis as Group 2. Exclusion criteria included patients having control coronary angiography within 3 months of the first procedure (n=7), creatinine level exceeding 1.5 mg/dl or calculated GFR <60 ml/min (n=25), any contraindication to coronary angiography (n=1), and patients under vitamin D supplements for various indications such as osteoporosis (n=29). This study was approved by our Institutional Review Board. Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

Coronary angiography

Selective coronary angiography was performed via the femoral or radial route by the Judkins technique. Two experienced interventional cardiologists blinded to the study protocol evaluated the coronary angiography results. With the contrast-filled injection catheter as the calibration source, stenosis % was measured by quantitative angiography on digital angiograms by use of a validated automated edge detection algorithm. An unforeshortened angiographic projection with minimal degree of vessel overlap displaying the restenosis in its sharpest and tightest view was used for analysis in acquired images. Binary restenosis was defined as a stenosis diameter of ≥50% in stented segment of the vessel.

Laboratory measurements

Just after selective coronary angiography, venous blood samples were drawn from the patients for analyses of the serum 25(OH)D3 levels. Fasting plasma glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and creatinine were determined by using standardized methods. Serum 25(OH)D3 was determined by reverse-phase HPLC. The intraassay percent coefficient of variation for this assay ranges from 1.9% at a 25(OH)D3 concentration of 61.5 ng/ml to 6.3% at a 25(OH)D3 concentration of 14.3 ng/ml. The interassay percent CV is 3.2% at a 25(OH)D3 concentration of 59.8 ng/ml and 3.9% at a 25(OH)D3 concentration of 14.3 ng/ml. Normal reference values of our laboratory were 20.0-120.0 ng/ml.

Statistical analysis

Data were analyzed using SPSS 15.0 for Windows. Continuous variables were expressed as mean ± SD and categorical variables as percentages. Kolmogorov-Smirnov test was used for testing distribution of the data. Student's t test was used for normally distributing variables and Mann-Whitney U test for variables without normal distribution. Multivariate logistic regression analysis was used whether serum 25(OH)D3 is an independent risk factor for in-stent stenosis. A two-tailed p value < 0.05 was regarded as significant.

Results

Baseline clinical, demographic and laboratory characteristics of both groups were outlined in Table 1. Deficiency (<20 ng/mL) and insufficiency (<30 ng/mL) of 25(OH)D3 were common among our study population (107 patients 59% and 170 patients 93%, respectively). In Group 1, levels of 25(OH)D3 were lower (17.7 ± 5.3 ng/ml and 20.9 ± 6.7 ng/ml, p<0.001, respectively) and length of stent was longer than in Group 2 (18.7 ± 5.3 mm and 17.1 ± 11.2 mm, p<0.001, respectively). Other parameters were comparable in Group 1 and 2. Variables found to be statistically significant in univariate analysis between Group 1 and 2 were entered into multivariate logistic regression analysis. After multivariate analysis, level of vitamin D and stent length were independent predictors of BMS in-stent stenosis (Table 2). Considering to the ROC curve analysis, the best cutoff value of vitamin D for estimating in-stent restenosis was <16.9 ng/dl (AUC 0.618, p=0.006, Figure 1).

Table 1. Baseline clinical, demographic and laboratory characteristics of study groups.

Characteristics	Group 1 (n = 106)	Group 2 (n = 75)	P value
Age, years	60.5 ± 9.8	63.5 ± 9.8	0.06
Male sex, n (%)	70 (66%)	52 (69%)	0.62
Diabetes mellitus, n (%)	50 (47%)	30 (40%)	0.35
Hypertension, n (%)	57 (53%)	45 (60%)	0.44
Hyperlipidemia, n (%)	53 (50%)	47 (63%)	0.17
Family history of CAD, n (%)	36 (34%)	24 (32%)	0.87
Smoking, n (%)	38 (35%)	19 (25%)	0.14
Vessel for intervention			0.34
LMCA, n (%)	0 (0%)	1 (1%)	
LAD, n (%)	45 (43%)	37 (50%)	
Cx, n (%)	31 (30%)	19 (26%)	
RCA, n (%)	28 (26%)	16 (21%)	
Stenosis location			0.60
Proximal, n (%)	57 (54%)	36 (49%)	
Mid-segment, n (%)	36 (34%)	30 (41%)	
Distal, n (%)	11 (10%)	7 (9%)	
Body mass index, kg/m2	29.2 ± 11.8	28.3 ± 5.5	0.62
Fasting plasma glucose, mg/dl	127 ± 52	133 ± 66	0.69
Creatinine, mg/dl	0.94 ± 0.22	0.93 ± 0.25	0.85
Total cholesterol, mg/dl	168 ± 41	176 ± 41	0.11
LDL cholesterol, mg/dl	96 ± 35	104 ± 39	0.07
HDL cholesterol, mg/dl	38 ± 9	38 ± 9	0.74
Triglycerides, mg/dl	157 ± 65	168 ± 93	0.97
Follow-up period, days	580	795	0.35
Stent diameter, mm	2.90 ± 0.36	2.93 ± 0.37	0.76
Stent length, mm	18.7 ± 5.3	17.1 ± 11.2	<0.001
Vitamin D level, ng/dl	17.7 ± 5.3	20.9 ± 6.7	<0.001

Abbreviations: CAD, coronary artery disease; LMCA, left main coronary artery; LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; LDL, low density lipoprotein ; HDL, high density lipoprotein

Table 2. Multivariate analysis of determinants of in-stent stenosis in study patients.

Variable	Mulivariate analysis	
	Odds ratio, 95% CI	p Value
Age	0.975 (0.945-1.006)	0.111
Low density lipoprotein	0.993 (0.985-1.002)	0.107
Stent length	1.038 (1.007-1.078)	0.026
Vitamin D level	0.924 (0.874-0.976)	0.005

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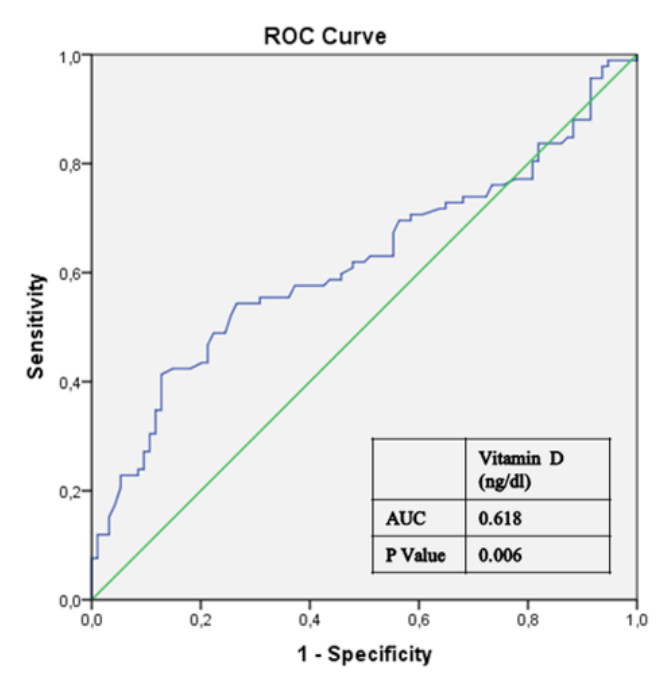

Figure 1: Receiver operator characteristic (ROC) curve of Vitamin D level for the development of bare-metal is-stent restenosis.

Discussion

To our knowledge, this is the first study to evaluate the relationship between levels of 25(OH)D3 and in-stent stenosis in patients with SCAD. Our observations suggest that low levels of 25(OH)D3 are associated with an increased risk of in-stent stenosis.

Percutaneous coronary intervention (PCI) with stenting has become a standard treatment option for coronary artery disease (CAD). In-stent stenosis after PCI remains a challenging clinical problem. The main mechanism responsible for restenosis is neointimal proliferation, which is caused primarily by the effects of vascular smooth muscle cell proliferation.[8]

This cell proliferation after stent implantation occurs both early, as part of the acute injury response, and late, due to inflammatory response. Although some neointima formation is necessary for vessel healing after stenting to prevent exposure to the formed blood elements such as platelets, excessive neointima formation, neointimal hyperplasia, causes stenosis and narrows the luminal area of the stent.[9] The vascular endothelium plays a central role in maintaining vascular hemostasis via its anti-inflammatory and antithrombotic properties.[10]

Vitamin D induces the production of prostacyclin by vascular smooth muscle cells, which prevents thrombus formation, cell adhesion, and smooth muscle cell proliferation.[11] Vitamin D can directly affect the development of CAD with some possible mechanisms including reduction in inflammation, suppression of the renin-angiotensin-aldosteron system, and modulation of cardiovascular remodeling. Also vitamin D acts as a direct factor on cardiac tissues and the vasculature. In vitro and in vivo studies have evaluated its role acting directly on cardiac tissue, especially in response to injury. Vitamin D inhibits pro-fibrotic inflammatory markers, suggesting that vitamin D might also have a direct effect on the vascular tissue in response to injury.[12] In a double-blind, randomized, placebo-controlled trial of vitamin D supplementation (a daily supplement of 50 ng (2000 IU) cholecalciferol) in subjects with congestive heart failure demonstrated significant reductions in inflammatory cytokines.[13] Therefore, Vit D may reduce cardiovascular risk by inhibiting vascular smooth muscle proliferation via decreasing calcium cellular influx and increasing matrix Gla protein and reducing inflammation via inhibiting cyclooxygenase 2 pathway, matrix metalloproteinase 9 and several proinflammatory cytokines.[14] Vitamin D induces its nuclear receptor and modulates related transcription factors resulting in anti-fibrotic signaling pathways in smooth muscle cells characterized by inhibiting expression of pro-fibrotic markers and increasing expression of anti-fibrotic markers leading to an effective reduction in collagen synthesis, and supports the emerging clinical findings linking vitamin D deficiency to adverse cardiovascular events.[15]

Al Mheid et al. showed that vitamin D insufficiency was associated with increased arterial stiffness and endothelial dysfunction in healthy humans.[16] Investigators found that vitamin D supplementation improves endothelial function, in patients with diabetes and in healthy adults with vitamin D-insufficiency.[17,18] Motiwala et al have recently reviewed prospective cohort and randomized clinical trials that studied the association between serum vitamin D and CVD.[19] A low level of serum 25 (OH)D3 has been found as a risk factor for CAD and cardiovascular death. In addition, multiple recent epidemiologic and prospective studies have showed a strong association between vitamin D insufficiency and risk of CVD, diabetes mellitus, metabolic syndrome, obesity, hypertension, peripheral vascular disease, ischemic heart disease, sudden cardiac death, and heart failure.[20-24]

It was recently demonstrated that serum 25(OH)D3 levels are

inversely associated with coronary lesion severity established by coronary angiography.[25] This data suggests that vitamin D may play a role in the development and progression of atherosclerosis. These findings should be confirmed by larger trials and determined whether vitamin D supplementation prevent the development of CVD. Prospective, randomized and placebo-controlled studies evaluating the effect of vitamin D supplementation on in-stent stenosis are needed before the use of this therapy for patients who have received a stent.

Study limitations

One of the major limitations of our study was limited sample size. Second, only patients with anginal complaints or ischemia demonstrated with non-invasive tests were taken in the study. Moreover in-stent restenosis were not evaluated by vascular imaging such as IVUS or OCT. Our study was an observational cross-sectional study that a causative association between serum vitamin D and in-stent stenosis cannot be defined. Geography, seasonality, latitude, and altitude presumably as a result of sunlight exposure can influence levels of vitamin D. 25(OH)D3 has a relatively long circulating half-life (approximately 3 weeks) and is considered a good biomarker, but serum vitamin D levels may change throughout the day and season of the year. A single measurement of vitamin D may not reflect lifetime status, and coronary atherosclerosis progresses over many years. The reason for the lower range of serum vitamin D levels in our study was explained probably with the minimum effect of the sunlight exposure between the autumn and winter months. On the other hand, we did not evaluate uric acid, hs-CRP, monocytes, lymphosites and other inflammatory markers which contribute development of CAD.

Conclusion

Low level of Vitamin D might be related to fibrosis and inflammation resulting in in-stent stenosis. Further studies are warranted to determine whether vitamin D supplementation could prevent progression of stent restenosis.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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To cite this article: Cokmez H, Aydin C. Comparison between pregnant Syrian refugees and Turkish residents in terms of a history of multiple cesarean sections. Turk J Clin Lab 2020; 4: 243-249.

Original Article

Comparison between pregnant Syrian refugees and Turkish residents in terms of a history of multiple cesarean sections

Geçirilmiş multipl sezaryen öyküsü bakımından Suriyeli mülteci ve yerleşik Türk vatandaşı gebelerin karşılaştırılması

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Abstract

Aim: To compare pregnancy outcomes between pregnant Syrian refugees and Turkish citizens with a history of multiple cesarean sections.

Material and Methods: The pregnant women included in this retrospective cohort study were Syrian refugees and resident Turkish citizens with a history of multiple cesarean sections who were admitted between January 1 2017 and August 1 2018 in a tertiary hospital. All data about the demographics, multiple cesarean numbers, emergent/elective cesarean numbers, hematocrit values, and neonatal birth weights were comparatively analyzed between the two groups.

Results: The Syrian refugee group had a higher ratio of women with a history of >2 cesarean sections than the Turkish citizen group (23.2% vs 11.1%, $p<0.05$). The ratio of urgent cesarean section operations were higher in the Syrian refugee group than in the Turkish citizen group (69.6% vs 55.4%, $p<0.05$). The Syrian refugee group had longer pregnancy duration (39.08±1.01 vs 38.46±1.50 weeks, $p<0.001$) and lower neonatal birth weights (3117.83±363.36 g vs 3230.93±472.67 g, $p<0.05$).

Conclusion: Our data suggested a significant relationship between a history of >2 cesarean sections and the pregnant Syrian refugees. The Syrian refugees had longer pregnancy duration, lower neonatal birth weights, and a higher rate of emergency cesarean sections. Therefore, we think that complications related to caesarean section may increase gradually over time in Syrian refugee pregnant women.

Keywords: refugees; pregnancy outcome; prenatal care; cesarean section

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Recevied: 02.01.2020 accepted: 22.02.2020
Doi: 10.18663/tjcl.669555

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Öz

Amaç: Suriyeli mülteci ve yerleşik Türk vatandaşı gebelerin, gebelik sonuçlarını geçirilmiş sezaryen sayısı bakımından karşılaştırmak.

Gereç ve Yöntemler: Bu retrospektif kohort çalışmaya 1 Ocak 2017 ile 1 Ağustos 2018 tarihleri arasında, üçüncü basamak bir hastanede sezaryen doğumu gerçekleşmiş, multiple sezaryen öyküsüne sahip Suriyeli mülteci ve yerleşik Türk vatandaşı gebeler dahil edildi. İki grup demografik veriler, geçirilmiş sezaryen sayıları, acil/elektif sezaryen sayıları, hematokrit düzeyleri ve yenidoğan ağırlıkları bakımından karşılaştırılarak analiz edildi.

Bulgular: Suriyeli mülteci gebeler arasında >2 multiple sezaryen öyküsüne sahip kadın oranı yerleşik Türk vatandaşları gebelerden fazlaydı (sırasıyla, %23,2; %11,1; p<0,05). Acil sezaryen doğum oranı Suriyeli mülteci gebelerde yerleşik Türk vatandaşı gebelere göre daha fazlaydı (sırasıyla %69,6; %55,4; p<0,05). Suriyeli mülteci grubu daha uzun gebelik süresine (39,08 ± 1,01 vs. 38,46 ± 1,50 hafta, p <0,001) ve daha düşük yenidoğan doğum ağırlığına (3117,83 ± 363,36 g vs. 3230,93 ± 472,67 g; p <0,05) sahipti.

Sonuç: Bulgularımız >2 sezaryen öyküsü ile Suriyeli mülteci gebeler arasında anlamlı bir ilişki olduğunu göstermiştir. Suriyeli mültecilerde gebelik süresi daha uzundu, yenidoğan doğum ağırlıkları daha düşüktü ve daha yüksek acil sezaryen oranları mevcuttu. Bu nedenle, Suriyeli mülteci gebelerde sezaryen ile ilişkili komplikasyonların zaman içerisinde giderek artabileceğini düşünüyoruz.

Anahtar kelimeler: mülteciler; gebelik sonuçları; prenatal bakım; sezaryen

Introduction

Turkey has accommodated the most number of Syrian refugees worldwide, with women aged between 19 and 24 years accounting for 640,000 of these refugees.[1] Studies involving different ethnic groups have shown that cases of poor maternal and fetal outcomes have increased in refugee communities.[2,3] Recent studies have revealed that pregnant Syrian refugees go into labor with lower hematocrit and hemoglobin levels than pregnant Turkish citizens.[4,5] Poor maternal outcomes are related to a history of more than 2 cesarean sections [6] and anemia [7] in both women. However, there has been no study that compared the number of cesarean sections and complications between pregnant Syrian refugees and settled Turkish citizens with a history of repeated cesarean sections.

The aim of this study was to compare the pregnancy outcomes of pregnant Syrian refugees and Turkish citizens with a history of repeated cesarean sections.

Material and Methods

The data of this retrospective study were obtained by reviewing the hospital records of 340 pregnant women who had repeated cesarean deliveries between January 1, 2017 and August 1, 2018 in our institution. The study protocol was approved by the ethics committee of our institution (#336/2018). The study was performed in accordance with the ethical standards stipulated in the recent version of the 1964 Declaration of Helsinki, as revised in 2013. Given the retrospective design of the study and anonymized data used in the analyses, informed consent was not obtained from the patients.

The patients included in the study were divided into the Syrian refugee and Turkish citizen groups. The demographic data, hematocrit values before and after cesarean delivery, operative durations, blood transfusion, obstetric complications (placental ablatio, placenta previa and acreata, pre-eclampsia, uterine atony), and neonatal birth weights were analyzed and compared between the two groups.

In our study, patients who were admitted to our institution with Syrian refugee identity card given by the Republic of Turkey were referred to as Syrian refugees. Patients who were admitted to our institution with "Turkish citizen ID card" given by the Republic of Turkey was referred to as resident Turkish citizens.

Pregnant women with a previous cesarean section were included

in the study. Furthermore, the cases were analyzed in terms of the number of previous cesarean sections and divided into the following two groups: those with a history of >2 cesarean deliveries and those with a history of ≤2 cesarean deliveries.

The hematocrit value was expressed as the percentage of packed erythrocytes detected by a whole blood count analyzer (XN-1000 analyzer, Sysmex, Kobe, Japan) in a venous blood sample taken into a tube with ethylenediamine tetraacetic acid. Preoperative hematocrit values for elective cases were obtained from routine hemogram results at 15 days before the cesarean section according to the protocol of our clinic. Preoperative hematocrit values for emergency cases were obtained from the results of the hemogram examination performed at the time of admission. Postoperative hematocrit value was obtained from the postoperative 24-hour hemogram examination results [8]. If erythrocyte suspension was applied to the patients for any reason in the period until admission to the clinic and routine postoperative 24-hour hemogram examination, postoperative hematocrit data were not included in the analysis.

The operation duration was determined from the data recorded in minute by a staff member in the operating room. This is the period from the time of the skin incision until the end of the skin suture. Operative duration was expressed in minutes.

The weight of the newborn was obtained from the data entered by the pediatric nurse after weighing the newborn in the electronic baby balance inside the operating room and recorded in grams in the patient file. Birth weight was expressed in grams.

Cesarean section was defined as elective cesarean section in women who had a scheduled cesarean section because of repeated cesarean indication from the obstetric clinic of our institution. Those with a history of multiple cesarean sections who were admitted to the emergency department and underwent cesarean section were referred to as cases of emergency cesarean section.

Pregnant women at ≥24 weeks gestation who had a cesarean section at our institution and had at least two antenatal follow-up visits in our outpatient clinic were included in the study. The birth week of the women whose last menstrual date data could not be found in the patient file was calculated according to the week determined according to fetal crown-rump length (CRL) measurements if the obstetric ultrasound was performed in the first trimester of pregnancy, and women without this data were excluded from the study. Pregnant women with chronic disease (Type 1 or 2 diabetes, rheumatologic or autoimmune disease, cardiovascular diseases, chronic infections) were excluded from the study. In addition, cases of multiple pregnancies were excluded. Patients who underwent myomectomy, adnexal cyst excision and scar revision during cesarean section were also excluded from the study to reduce the variation of operative durations.

Continuous data were expressed as mean ± standard deviation and categorical data were expressed as numbers and percentages. Continuous data with normal distribution were analyzed by Student's t-test and non-normally distributed continuous data were compared with Mann-Whitney U test. Categorical data were compared using Pearson's chi-squared and Fisher's exact tests. All calculations are based on IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY). Significance was evaluated at a minimum level of $p<0.05$.

Results

During the study period, among the 340 cases, 69 (20.3%) Syrian refugees and 271 (79.7%) Turkish citizens met the inclusion criteria. When all the cases were considered thoroughly, patients' median age was 29 (range: 17-43) years, median preoperative hematocrit value was 35% (range: 23%-43%), median postoperative hematocrit value was 32% (22%-42%), and the median operative duration was 50 (31-72) minutes. A total of 198 (58.2%) cases were emergency cesarean sections and 142 (41.8%) were elective cesarean sections. The numbers of obstetric complications for all the cases were as follows: 19 (5.6%) cases of atony, 5 (1.5%) cases of ablatio placenta, 8 (2.4%) cases of preeclampsia, and 1 (0.3%) case of subtotal placenta previa.

The outcomes, which were obtained as a result of comparing and separately analyzing the demographic, laboratory, and operative data of both groups, are shown in Table 1. Although the erythrocyte suspension was applied to 3 (4.3%) women in the Syrian refugee group and 15 (5.5%) women in the Turkish citizen group, no significant difference was observed between the two groups ($p=0.694$).

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Table 1. Comparison of the demographic, laboratory, and operative data between the Syrian refugee and Turkish resident groups				
		Syrian refugee	Resident Turkish citizens	P value
Age (mean ± SD)		27.10±5.47	30.5±5.46	<0.001
Gravida (n)		3.44±1.71	3.16±1.20	0.503
Parity (n)		2.15±1.32	1.83±0.95	0.182
Number of previous cesarean sections n (%)	≤ 2	53 (76.8)	241 (88.9)	0.009
	> 2	16 (23.2)	30 (11.1)	<0.001
Gestational age (week)		39.08±1.01	38.46±1.50	0.016
Neonatal birth weight (gram)		3117.83±363.36	3230.93±472.67	0.185
Hematocrit level (%)	Preoperative	34.06±3.29	34.65±3.61	0.039
	Postoperative	31.15±2.75	32.02±3.52	0.914
Operative duration (minute)		50.87±8.71	50.97±8.14	0.033
Operation type n (%)	Emergency	48 (69.6)	150 (55.4)	0.614
Obstetric complications		7 (11.6)	25 (9.2)	

In all women, 294 (86.5%) o have had ≤2 cesareans previously and 46 (13.5%) have had >two cesareans previously. The percentage distribution of Syrian refugees and Turkish citizens according to the history of cesarean sections (≤2vs >2) is presented in Figure 1.

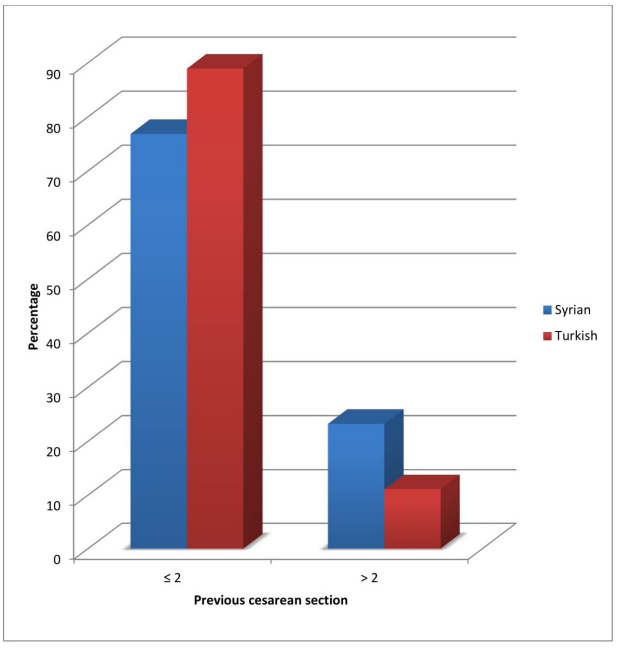

Figure1. Percentage distribution of pregnant Syrian refugees and resident Turkish citizens according to the number of previous cesarean section

The results of the comparative analysis of the average postoperative hematocrit levels and average operative durations between Syrian refugees and Turkish citizens are presented in Table 2.

Discussion

Our study is the first study that compared the maternal and fetal outcomes between Syrian refugees and resident Turkish citizens with a history of cesarean section. Our most important finding was that pregnant Syrian refugee women are more likely to have >2 previous cesarean sections compared to resident Turkish citizens. Before the Syrian civil war, Syria had a cesarean rate of 15.0%, ranging from 5.3% to 26.2% in the Arab region.[9] In a study investigating the cesarean section rate among Syrian refugees in Lebanon, the rate of cesarean section was found to be higher in Syrian refugees than in resident Lebanese citizens.[10] In the same study, this rate was caused by the limited access to adequate health services among Syrian refugees. Owing to the increasing number of Syrian refugees migrating in Turkey for the past 10 years, approximately 700,000 women aged 19-44 years are added to the national population.[1] In addition, Turkey has lesser number of medical doctors when compared to the proportion of the population in European countries.[11] Moreover, since

Table 2. Postoperative hematocrit level and operative times between women with a history of ≤2 cesarean sections and those women with a history of >2 cesarean sections in both the Syrian refugee and Turkish resident groups

	Syrian refugee			Resident Turkish citizens		
	Previous cesarean section ≤2	Previous cesarean section >2	p value	Previous cesarean section ≤2	Previous cesarean section >2	p value
Postoperative hematocrit (%)*	31.04±2.61	32.00±2.63	0.142	32.17±3.60	31.00±2.99	0.75
Operative duration (minute)	48.62±8.25	58.31±5.56	<0.001	50.09±8.05	58.33±5.71	<0.001

*Patients with erythrocyte suspension were not included in the analysis.

Syrian refugees continue to migrate in the country, they have lesser access to health care services than Turkish residents.[11] Indeed, Erenel et al.[5] found that Syrian refugees received lesser antenatal follow-up than Turkish residents. Moreover, in pregnant Syrian refugees, psychological traumas caused by war and migration [12] and fears about losing the baby during vaginal delivery are frequent.[13,14] Thus, over the years, these conditions may have led to an increase in the number of pregnant Syrian refugees with a history of cesarean section. Further, the tendency to have many children is high among Syrian women because of the value system of the Syrian society [15]. In our case series, two of the Syrian pregnant refugees had their fifth cesarean section. Moreover, Huster et al.[10] have also reported of a pregnant Syrian refugee who underwent a tenth cesarean operation at a health center in Lebanon.

In our study, when comparing the gestation periods between the two groups, Syrian refugees had significantly longer pregnancy duration. Moreover, we found that there were significantly more cases of emergency cesarean sections in the Syrian refugee group than in the Turkish citizen group. In our clinic, those with a history of cesarean section are scheduled for elective cesarean section after the 39th week of gestation. The inadequate antenatal follow-up among the pregnant Syrian refugees [5,16,17] may have caused the low rate of scheduled elective cesarean sections, which might have led to the longer average gestational age among Syrian refugees. Therefore, Syrian refugees may have undergone more emergency cesarean operations than the resident Turkish citizens. Despite the longer gestational age among Syrian refugees, the birth weight of their newborns was significantly lower, this finding was comparable to those of previous studies conducted in Turkey.[4,5,17,18]

In our study, no significant difference was found in placental dysfunctional diseases (placental ablation, pre-eclampsia, intrauterine growth retardation) between the two groups. In some studies comparing pregnant Syrian refugees with pregnant resident Turkish citizens, no difference was found in terms of poor pregnancy outcomes.[5,19]

Regarding age, The Syrian refugees were mostly younger, which are comparable to most studies [4,5,17], except that conducted by Gungor et al. [19] Moreover, Türkay et al.[18] and Alnuaimi et al.[20] found that adolescent pregnancies were significantly more frequent among Syrian refugees.

In countries hosting Syrian refugees, longer-term health policies, rather than immediate measures, are being established for this population.[21,22] Thus, this may have cause the lesser incidence of prepartum anemia among pregnant Syrian refugees investigated after 2016 [19] and even in current studies than those investigated before 2016.[5,17]

In terms of postpartum hematocrit values, a significant difference was found between those women with a history >2 cesarean sections and those women with a history <2 cesarean sections in both groups. Women with a history of >2 cesarean sections had significantly longer operative time than those with a history ≤2 cesarean sections. However, the postpartum hematocrit values did not differ between the two groups, indicating that the postpartum hematocrit values are not related to operative time or the number of previous cesarean sections.

The strength of our study are as follows: no patient had missing data in their files owing to the presence of translators in our hospital during the study period, and our study was the first study that have compared pregnant Syrian refugees and Turkey citizens with a history of previous cesarean section. However, our study has several limitations. Our study had a retrospective

design and sample size owing to our strict inclusion and exclusion criteria. Neonatal outcomes data were limited due to the lack of on-call pediatricians and neonatal intensive care units. We believe that more studies are needed to investigate the effect of this relationship on pregnancy outcomes.

Conclusion

Among Syrian refugees the higher number of a history of >2 cesarean sections observed. Therefore, we consider that cesarean section related complications may increase gradually over time in Syrian refugee pregnant women.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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To cite this article: Ulucakoy C, Yapar A. Diagnostic role of NLR, MLR and PLR in patients with lipoma and liposarcoma. Turk J Clin Lab 2020; 4: 250-254.

Original Article

Diagnostic role of NLR, MLR and PLR in patients with lipoma and liposarcoma

Lipom ve liposarkomlu hastalarda NLR, MLR ve PLR'nin tanısal rolü

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Abstract

Aim: The aim of this study is to investigate the diagnostic role of Neutrophil-to-lymphocyte ratio (NLR), Monocyte-to-lymphocyte ratio (MLR) and Platelet-to-lymphocyte ratio (PLR) in patients with lipoma and liposarcoma.

Material and Methods: Patients operated for lipoma and liposarcoma at our institution between 2015 and 2019 were included in this retrospective study. A total of 92 patients with 44 lipoma and 48 liposarcoma were included in this study. The results of the complete blood count before treatment were retrospectively analyzed. 94 patients with complete blood count results admitted to the same center for reasons other than fracture, infection or tumors with similar age and sex to the aforementioned study group were included as healthy controls.

Results: The average age of lipoma, liposarcoma and control groups included in the study was 55.3 ± 11.6, 48.9 ± 14.7 and 52.1 ± 11.7, respectively. While 50% of lipomas are located on the thigh and 40.9% are on the shoulder, 72.9% of the liposarcomas are located on the thigh. NLR values of the liposarcoma group were significantly higher than the control group. It was observed that PLR values did not differ significantly between groups. It was noted that MLR values were statistically significantly higher in the liposarcoma group than in the lipoma group. A significant but weak AUC value (AUC = 0.620, p = 0.020) was obtained for NLR. When the cut-off value and sensitivity, specificity, + LHR, PPV and NPV values of these cut off values are examined, NLR 1.83 and above values; It pointed out that his predictability was poor in the diagnostic approach for liposarcoma.

Conclusion: Consequently, lipoma and liposarcoma are the most common forms of benign and malignant soft tissue tumors. NLR and MLR may be valuable in the diagnosis of liposarcoma, but more studies are needed in this regard.

Keywords: Lipoma, Liposarcoma, Neutrophil-to-lymphocyte ratio; Monocyte-to-lymphocyte ratio; Platelet-to-lymphocyte ratio

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Recevied: 20.05.2020 accepted: 21.08.2020
Doi: 10.18663/tjcl.739589

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ÖZ

Amaç: Bu çalışmanın amacı, lipoma ve liposarkomlu hastalarda Nötrofil / lenfosit oranının (NLR), Monosit / lenfosit oranının (MLR) ve Trombosit-lenfosit oranının (PLR) tanısal rolünü araştırmaktır.

Gereç ve Yöntemler: 2015-2019 yılları arasında kurumumuzda lipom ve liposarkom nedeniyle opere edilen hastalar bu retrospektif çalışmaya alındı. Bu çalışmaya 44 lipoma ve 48 liposarkomlu 92 hasta dahil edildi. Tedaviden önce tam kan sayımı sonuçları geriye dönük olarak analiz edildi. Yukarıda belirtilen çalışma grubuna benzer yaş ve cinsiyete benzer kırık, enfeksiyon veya tümörler dışındaki nedenlerle aynı merkeze kabul edilen tam kan sayımı sonuçları olan 94 hasta sağlıklı kontroller olarak dahil edildi.

Bulgular: Çalışmaya dahil edilen lipom, liposarkom ve kontrol gruplarının yaş ortalaması sırasıyla 55.3 ± 11.6, 48.9 ± 14.7 ve 52.1 ± 11.7 idi. Lipomların% 50'si uylukta,% 40.9'u omuzda bulunurken, liposarkomların% 72.9'u uylukta bulunur. Liposarkom grubunun NLR değerleri kontrol grubundan anlamlı olarak yüksekti. PLR değerlerinin gruplar arasında anlamlı farklılık göstermediği gözlendi. Lipozarkom grubunda MLR değerlerinin lipoma grubuna göre istatistiksel olarak anlamlı derecede yüksek olduğu kaydedildi. NLR için anlamlı fakat zayıf bir AUC değeri (AUC = 0.620, p = 0.020) elde edildi. Bu kesme değerlerinin kesme değeri ve duyarlılığı, özgüllüğü, + LHR, PPV ve NPV değerleri incelendiğinde NLR 1.83 ve üzeri değerler; Liposarkom için tanısal yaklaşımda öngörülebilirliğinin zayıf olduğuna dikkat çekti.

Sonuç: Sonuç olarak, lipom ve liposarkom, benign ve malign yumuşak doku tümörlerinin en yaygın formlarıdır. NLR ve MLR, liposarkom tanısında değerli olabilir, ancak bu konuda daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Lipom; liposarkom; nötrofil-lenfosit oranı; monosit-lenfosit oranı; trombosit-lenfosit oranı

Introduction

Lipomas are very common benign neoplastic mesenchymal tumors arising from adipose tissue, while liposarcomas are the most common soft tissue sarcomas in adults and make up about 20% of all soft tissue malignancies.[1] While lipomas are limited masses of mature adipocytes that do not show cellular atypia, liposarcomas originate from primitive mesenchymal cells with much potential rather than mature adipose tissue.[2] Liposarcomas usually originate from the extremities, especially the thigh, retroperitoneum, groin and paratesticular areas.[3, 4] Differential diagnosis is performed clinically, radiologically and pathologically, but the need for a reliable and easily generalizable criteria is evident however there are no specific biomarker available in the clinical setting despite ongoing studies.[5]

The tumor microenvironment and, in particular, the inflammatory response play an important role in cancer development and progression and may be associated with systemic inflammation. [6] Recently, some inflammation parameters, originated from routine complete blood count (CBC), have been investigated as potential biomarkers with mixed results and no consensus so far regarding its accuracy and clinical usefulness: neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR). [7] Therefore, we aimed to investigate the diagnostic role of NLR, MLR and PLR in patients with lipoma and liposarcoma in this study.

Material and Methods

Patients diagnosed with lipoma and liposarcoma in our institution between 2015 and 2019 were included in this retrospective study. Ninety-two patients were identified in the institutional patient database and age, sex, location and type of tumor, pre-treatment complete blood count results were acquired retrospectively. Of 92 identified patients (51 males, 41 females) 44 were diagnosed with lipoma and 48 with liposarcoma. Ninety-four with complete blood count results admitted to the same center for reasons other than fracture, infection or tumors with similar age and sex to the aforementioned study group were included as healthy controls. Patients without necessary information or with high c-reactive protein or procalcitonin were excluded from the study. NLR.MLR and PLR were calculated as the absolute count of neutrophil,monocyte and platelet, respectively, divided by the absolute lymphocyte count. This study was approved

by our Institutional Review Board. Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

Statistical analysis

Statistical analyses were done using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics are presented as numbers and percentages for categorical variables and mean ± standard deviation, median (minimum value – maximum value) for continuous variables. Normal distribution for continuous variables were assessed with visual (histograms and probability graphics) and analytic methods (Kolmogorov-Smirnov and Shapiro-Wilk's test). In the data that do not fit the normal distribution, Mann-Whitney U test was used for comparison analysis between the two independent groups. Comparison analyses for categorical variables between independent groups were done by chi-square test.Diagnostic and prognostic values of pre-treatment NLR was assessed using receiver operating curve (ROC) analysis. The area under the ROC curve (AUC) results were considered excellent for AUC values between 0.9-1, good for AUC values between 0.8-0.9, fair for AUC values between 0.7-0.8, poor for AUC values between 0.6-0.7 and failed for AUC values between 0.5-0.6 (1,2). Results following ROC analysis; area under curve (AUC) and cut-off values, sensitivity and specificity of these cut-offs values, likelihood ratio PPD and NPD are presented. $P < 0.05$ was considered to be statistically significant.[8, 9]

Results

A total of 92 patients with 44 lipoma and 48 liposarcoma were included in this study. While 50% of lipomas are located on the thigh and 40.9% on the shoulder, 72.9% of the liposarcomas are located on the thigh (table 1). All lipomas were removed by excision and all liposarcomas were removed by wide resection. Comparison analysis of the control group included in the study with both patient groups are presented in table 2. While the gender distribution of the control group and lipoma and liposarcoma patients were similar ($p = 0.081$ and 0.314), it was observed that male patients were more frequent in the liposarcoma group than the lipoma group ($p = 0.013$). Age of liposarcoma group was significantly lower than lipoma group ($p = 0.013$). It was observed that the NLR values of the liposarcoma group were significantly higher than the control group ($p = 0.020$). PLR values did not differ significantly between the groups ($p = 0.110$, $p = 0.931$ and 0.159). It was noted that MLR values were statistically significantly higher in liposarcoma group than lipoma group ($p = 0.035$) (table 2).

Table 1. Basal Demografics of Malignancies

Characteristic	Total N=92	Lipoma n=44 (%47.8)	Liposarcoma n=48 (%52.2)
Localization, n (%)			
Thigh	57(62.0)	22(50.0)	35(72.9)
Shoulder	21(22.8)	18(40.9)	3(6.3)
Cruris	4(4.3)	0	4(8.3)
Gluteal Region	3(3.3)	0	3(6.3)
Elbow	2(2.2)	2(4.5)	0
Forearm	2(2.2)	2(4.5)	0
Arm	2(2.2)	0	2(4.2)
Back	1(1.1)	0	1(2.1)
Direction, n(%)			
Right	56(60.9)	28(63.6)	28(58.3)
Left	36(39.1)	16(36.4)	20(41.7)
Surgery, n (%)			
Excision	44(47.8)	44(100)	0
Wide Resection	48(52.2)	0	48(100)

Since NLR showed significant differences in liposarcoma and control group comparison analyzes, we evaluated the diagnostic predictability for liposarcoma with ROC analysis (fig 1). According to Table 3, a significant but weak AUC value (AUC = 0.620, $p = 0.020$) was obtained for NLR. When the cut-off value and sensitivity, specificity, + LHR, PPV and NPV values of these cut off values are examined, NLR 1.83 and above values; It pointed out that his predictability was poor in the diagnostic approach for liposarcoma (Sensitivity = 56.3%, specificity = 60%, + LHR = 1.4, PPV = 41.5% and NPV = 72.7) (Table 3).

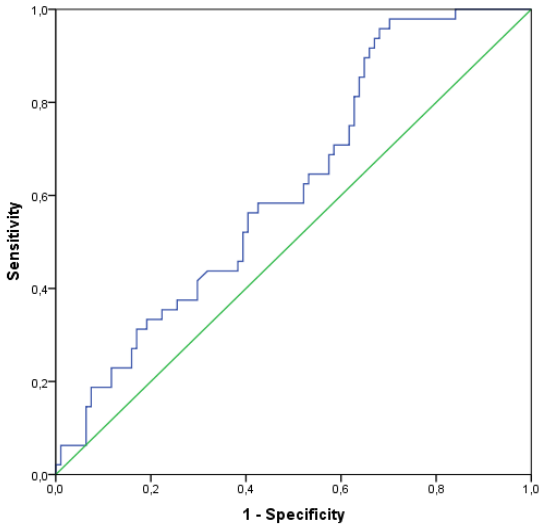

Figure 1. Receiver operating characteristic (ROC) curve for the NLR

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Table 2. Evaluation of Case-Control Groups

Characteristic	Control (G1) n=94	Lipoma (G2) n=44	Liposarcoma(G3) n=48	P (G1 vs. G2)	P (G1 vs. G3)	P (G2vs. G3)
Gender, n(%) Male Female	 55(58.5) 39(41.5)	 18(40.9) 26(59.1)	 33(68.8) 15(31.2)	0.0811	0.3141	0.0131
Age, Years Mean±sd Median(min-max)	 52.1±11.7 54.5(19-74)	 55.3±11.6 57(28-71)	 48.9±14.7 49(20-80)	0.0672	0.0782	0.0132
Hgb Mean±sd Median(min-max)	 14.5±1.5 14.9(10.6-17.1)	 13.7±1.5 13.4(11.2-16.4)	 13.9±1.9 14.7(7.5-16.2)	0.0012	0.0742	0.0582
NLR Mean±sd Median (min-max)	 1.87±0.89 1.73(0.11-6.22)	 2.24±1.1 1.80(0.88-4.26)	 2.44±2.25 1.84(1.13-16.79)	0.1292	0.0202	0.6502
PLR Mean±sd Median(min-max)	 126.6±39.3 116.9(63.7-296.7)	 138.4±45.9 140.9(64.1-244.5)	 132.8±70.7 125.1(30.9-507.6)	0.1102	0.9312	0.1592
MLR Mean±sd Median(min-max)	 4.93±1.47 4.80(1.55-9.13)	 4.84±2.0 4.3(1.79-10.31)	 5.12±1.54 5.03(0.77-7.62)	0.1542	0.2032	0.0352

1Chi-Square Test
2Mann-Whitney U test

Table 3. Diagnostic value of NLR for liposarcoma

	AUC (95% CI)	P	Cut-off	Sensitivity (%)	Specificity (%)	+LHR	PPV (%)	NPV (%)
NLR	0.620 (0.527-0.713)	0.020	≥1.83	56.3	60	1.4	41.5	72.7

+LHR: Positive Likelihood Ratio, PPV: Positive Predictive Value, NPV: Negative Predictive Value

Discussion

Lipoma and liposarcoma are the most common benign and malignant soft tissue tumors, respectively. [1] Our study shows that NLR and MLR can be useful in the differential diagnosis of lipoma and liposarcoma.

The relationship between inflammation and tumors is well established. Inflammation can increase the risk of cancer and promote carcinogenesis. [10] Although it is not clearly understood which mechanisms cause this relationship, some theories have been suggested. Tumor-related inflammation may cause direct or indirect increases in cytokines, inhibition of apoptosis, and increases in angiogenesis. [11] Tumor cells release granulocyte colony-stimulating factor (GCSF) that can trigger neutrophilia. Neutrophils play a role in tumor angiogenesis by producing proangiogenic factors such as vascular endothelial growth factor, matrix metalloproteinase, interleukin-8, and elastases. [12]Based on this information, NLR, MLR and PLR, whose relationship with most cancer has been investigated; We investigated its role in the diagnosis of lipoma and liposarcoma.

Systemic inflammatory biomarkers such as NLR, MLR and PLR in clinical management of cancers have recently begun to emerge as viable alternatives to traditional methods that have been shown to be associated with diagnosis and / or prognosis in different tumor types.[13-16] Current interest in utilizing these ratios seem justified as these are readily available values derived from routine complete blood count with no economic burden. We recorded NLR, MLR and PLR values from the routine complete blood count.

Hu et al. In 2018, they showed increased NLR in hepatocellular cancer patients.[13] Similarly, Li et al. showed that NLR can be used as a diagnostic marker in colorectal cancer.[14] Also Kemal et al. found high NLR and PLR values in lung cancer patients compared to healthy volunteers.[15] Likewise Nikolić et al. In 2016, they showed that NLR and PLR values were significantly higher in patients with lung cancer. [16] In our study, the NLR value of the liposarcoma group was significantly higher compared to the control group.

This study has some limitations. First, a significant but weak cut-off value was found for NLR. Another limitation would be retrospective, single-center nature of the study. We believe that future studies with larger sample sizes are necessary to further explore the characteristics of inflammation and role of systemic inflammatory biomarkers in lipoma and liposarcoma.

Conclusion

Lipoma and liposarcoma are the most common forms of benign and malignant soft tissue tumors. NLR and MLR may be valuable in the diagnosis of liposarcoma, but more studies are needed in this regard.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Turkish Journal of Clinics and Laboratory

To cite this article: Kartal S, Gunaydin B, Barun S, Elmas C. Effects of isoflurane, ketamine and dantrolene on apoptosis in the rat hippocampus. Turk J Clin Lab 2020; 4: 255-261.

Original Article

Effects of isoflurane, ketamine and dantrolene on apoptosis in the rat hippocampus

Sıçan hipokampüsünde izofluran, ketamin ve dantrolenin apoptozis üzerine etkileri

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Abstract

Aim: Since both isoflurane and ketamine were already known to cause neurodegenerative apoptotic effects and dantrolene was known to inhibit degeneration, we investigated whether dantrolene could play a cytoprotective role under isoflurane and/or ketamine anesthesia. Therefore, we aimed to determine caspase activation as a marker of apoptosis in hippocampus (CA1 and dentate gyrus regions) of rats exposed to either administration of isoflurane with or without ketamine and dantrolene or isoflurane+ketamine+dantrolene.

Material and Methods: Thirty Wistar male rats were randomly assigned to five groups. Only oxygen 100% was administered into the closed cage for 2 hours in the control group (group A) whereas in the four study groups (as B,C,D and E), either 1.4% isoflurane alone in 100% oxygen was administered (group B) or 1.4% isoflurane in 100% oxygen was administered 60 minutes after intraperitoneal (ip) injection of dantrolene 10 mg/kg (group C), subcutaneous (sc) ketamine 40 mg/kg (group D) or ip dantrolene + sc ketamine (group E). Rats were sacrified to perform histopathologic and immunohistochemical analysis (hematoxylin staining caspase activation).

Results: Isoflurane alone (group B) and isoflurane+ketamine (group D) exposure to rats resulted in a significantly increased caspase activation when compared to control (group A) and dantrolene inhibited isoflurane + ketamine induced apoptosis in the hippocampus.

Conclusion: Isoflurane with or without ketamine caused neuroapoptosis in rats and dantrolene attenuated the apoptotic effect of both isoflurane and isoflurane+ketamine by decreasing caspase activation. These results might have an important promising role in anesthetic choice for specific susceptible group after further clinical studies.

Key words: Isoflurane; ketamine; dantrolene; apoptosis

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Recevied: 23.08.2020 accepted: 10.09.2020
Doi: 10.18663/tjcl.782524

Öz

Amaç: Hem izofluran ve ketaminin nörodejeneratif apoptotik etkileri gösterilmiş hem de dantrolenin dejenerasyonu inhibe ettiği bilindiği için biz izofluran ve/veya ketamin anestezisi altında dantrolenin sitoprotekif bir rolü olup olamayacağını araştırdık. Bu nedenle sıçan hipokampüsünde (CA1 ve dentat girus bölgelerinde) apoptozisin belirteci olan kaspaz aktivasyonunu; izofluranı ketamin ve dantrolen varken veya yokken veya izofluran+ketamin+dantrolen varlığında belirlemeyi amaçladık

Gereç ve Yöntemler: Wistar 30 erkek sıçan rastgele beş gruba ayrıldı. Kontrol grubunda (grup A) 2 saat sadece %100 oksijen verilirken, çalışma grubunda (B, C, D ve E) ya sadece %100 oksijen içinde %1.4 izofluran (grup B) veya intraperitoneal (ip) dantrolen 10 mg/kg enjeksiyonundan (grup C), subkutan (sk) ketamin 40 mg/kg enjeksiyonundan (group D) ya da ip dantrolen + sk ketamine enjeksiyonundan (group E) 60 dk sonra %100 oksijen içinde %1.4 izofluran uygulanmıştır. Sonra sıçanlar histopatolojik ve immunohistokimyasal inceleme (hematoxylin boyama ile kaspas aktivasyonu) için sakrifiye edilmişlerdir.

Bulgular: Sadece izofluran (grup B) ve izofluran+ketamine (grup D) maruz kalan sıçanlarda kontrol grubuna (grup A) göre hipokampüsde kaspas aktivasyonunda önemli artış ile dantrolenin izofluran+ketaminle indüklenmiş apoptozisi inhibe ettiği gözlendi.

Sonuç: İzofluranın ketamine varken ya da yokken sıçanda nöroapoptozise neden olduğu ve dantrolenle; izofluran ve izofluran+ketaminin apoptotik etkisinin azalan kaspaz aktivasyonuyla olduğu gösterilmiştir. Bu sonuçlar ileri klinik çalışmalardan sonra duyarlı grupların anestezi seçimde rol oynabilir.

Anahtar kelimeler: Izofluran; ketamin; dantrolen; apoptozis

Introduction

Neurodegeneration in developing animals following exposure to anesthetics has been established with intravenous or inhalational anesthetics [1]. Among commonly used general anesthetics in practice, isoflurane and ketamine were associated with neurodegenerative apoptotic effects [2-5]. Based on the biochemical evidences, caspase activation in execution of apoptosis include initiation of either intrinsic or extrinsic pathway. Both pathways converge at the activaton of effector caspase-3 which cleaves several cellular proteins, finally leading to apoptosis [6]. Additonally, isoflurane induced apoptosis was inhibited by dantrolene. Thus, a pivotal cytoprotective role for dantrolene, which is a ryanodine receptor antagonist drug specifically used to treat malign hyperthermia has been considered [7]. Therefore, we aimed to investigate whether dantrolene could play a cytoprotective role under isoflurane anesthesia with or without ketamine by determining caspase activation as a marker of apoptosis in hippocampus (CA1 and dentate gyrus regions) of rats.

Material and Methods

After obtaining approval of Gazi University Animal Experiments Local Ethics Committee (Resaerch Project number G.Ü.E.T-10.088), all procedures was carried out in accordance with the 'Care and Use of Laboratory Animals' rules, 30 young adult male Wistar rats weighing approximately 200±25 gram were housed with access to food and water in special cages at 21±1°C within a room adjusted 12:12 hour (h) light–dark cycle with lights on at 6 am for 7 days before the onset of study. Afterwards rats were randomly assigned to five groups as control (group A) and four study groups to administer either isoflurane alone (group B), isoflurane+dantrolene (group C), isoflurane+ketamine (group D) or isoflurane+ketamine+dantrolene (group E) in order to investigate early apoptosis by detecting caspase activation (caspase 3, 8 and 9).

1. Group A (n=6)

Only 100% O2 was administered at 4 L/minute (min) for 2 hours in the control group.

2. Group B (n=6)

1.4% isoflurane in 100% O2 at 4 L/min was administered for 2 hours.

3. Group C (n=6)

Sixty minutes (min) after intraperitoneal (ip) injection of dantrolene 10 mg/kg, 1.4% isoflurane in 100% O2 at 4 L/min was administered for 2 hours.

4. Group D (n=6)

Sixty min after subcutaneous (sc) injection of ketamine 40 mg/kg, 1.4% isoflurane in 100% O2 at 4 L/min was administered for 2 hours.

5. Group E (n=6)

Sixty min after ip injection of dantrolene 10 mg/kg and sc injection of ketamine 40 mg/kg, 1.4% isoflurane in 100% O2 at 4 L/min was administered for 2 hours.

Anesthesia procedure

In all groups spontaneous breathing was maintained in the closed cage which was considered as an anesthesia chamber having gas inlet and outlet. Oxygen and end-tidal isoflurane concentration in the chamber, heart rate and oxygen saturation were monitorized and rectal temperature of rats were kept approximately at 37.5 °C. All the experiments were performed at the same time (7 am). Pressured oxygen tank was connected to standard isoflurane vaporizator (Ohmeda® Isotec 3 Abbott) to deliver 1.4% isoflurane in 100% O2 at a flow rate of 4 L/min which was also connected to anesthesia chamber via a line. Gas analyser detector was connected to gas outlet of the anesthesia chamber. Both control and study groups were kept 6 hours within the steel cage during spontaneous breathing.

Sacrification procedure

After ip administration of ketamine 60 mg/kg, intracardiac blood samples were collected by the principal investigator and rats were sacrificed by exsanguination. Afterwards brain tissue was removed rapidly. Tissue samples were placed at pH 7.4 1/15 µ phosphate buffered 2.5% glutaraldehyde fixation solution for further electron microscope evaluation. After fixation, hippocampus was identified by vertical section. Tissue samples of 1 cm3 fixed in 10% neutral formalin for 72 hours were embedded in paraffin for further evaluation under light microscope.

Immunohistochemical procedure

Four µm sections of brain tissues based on polylsine-covered microscope slides from control group and study groups were subjected to immunohistochemical staining. Caspase activation to elucidate apoptosis was investigated in the hippocampus (CA1 and dentate gyrus regions).

Detection of caspase activation

Caspase-9 (Caspase-9 LAB6/Ab- 4) rabbit polyclonal antibody (Cat: RB- 1205-P, Lot:1205P306), caspase-8 (Caspase-8 FLICE/Ab-4) rabbit polyclonal antibody (Cat: RB-1200-P, Lot: 1200P708C) and caspase-3 (Caspase-3CPP32/Ab-4) rabbit polyclonal antibody (RB-1197-P, Lot: 1197P701) were applied. As a secondary kit, Ultravision Detection System Anti-Rabbit HRP (RTU) (Cat: TP- 125 HL, Lot: PBN70509, Lab Vision, Fremont, USA) and HRP/AEC (Cat: TA-007-HAC, Lot: 007HAC13565) were used.

Sections were kept overnight at 37^{0}C in oven and then temperature was raised to 57^{0}C for substracting the deparafinization and allowed for 1 hour. To complete the deparafinization process, slides were exposed to xylene for 15 min twice, respectively 100%, 96% and 80%. Afterwards alcohol with water was applied every 10 minutes followed by distilled water every 5 min twice to remove the alcohol.

For providing elucidation close to the receptor sites of formaldehyde, sections were performed to 1M citrate buffer in microwave (pH: 6. 0) (Cat: AP- 9003- 500, Lot: 9003LT13610, Lab Vision, Fremont, USA). After cooling room temperature within 20 minutes, endogenous peroxidase activity was blocked with hydrogen peroxide (Cat: TA-125-HP, Lot: 125HP14119, Lab Vision, Fremont, USA) for 15 minutes. Then, the cross sections were washed 3 times with PBS (Phosphate Buffer Saline) at pH: 7.4 after 3 minutes, epitopes were stabilized by application of serum blocking solution. Ultra V Block (Cat: TA-125-UB, Lot: AUB70803, Lab Vision, Fremont, USA) was applied for 5 minutes. Without washing, Caspase-8 (Cat: RB-1200-P, Lot: 1200P708C), Caspase-9 (Cat: RB-1205-P, Lot: 1205P306) and Caspase-3 (RB-1197-P, Lot: 1197P701) the primary antibodies were incubated for 60 minutes. The cross sections were washed 3 times with PBS at pH: 7.4 after 3 minutes. Then biotinylated secondary antibody (Cat: TR-125-BN, Lot: RBN70115, Lab Vision, Fremont, USA) was applied and streptavidin peroxidase (Cat: TS-125-HR, Lot: SHR70515, Lab Vision, Fremont, USA) was applied to the slides for 20 min.

After washing with PBS, AEC (3-amino-9-ethylcarbazole) (Cat:TA-007-HAC, Lot: 007HAC13565, Lab Vision, Fremont, USA) was used as chromogen to the sections. Finally, the slides were stained with Mayer's Hematoxylin (Cat: TA-125-MH, Lot: AMH70809, Lab Vision, Fremont, USA) and were covered with Ultramount (Cat: TA-125-UG, Lot: VM13518, Lab Vision, Fremont, USA). Slides were examined under light microscope (DM4000B Image Analyze System, Leica, Germany) and Leica DFC280 plus camera. The number of immune positive cells are measured manually by using Qwin software programme in consecutive areas for serial cutaways taken from. A semi-quantitative scoring system was used to assess the immunolabeling intensity as descibed.[8]

Statistical analysis

Statistical analysis was performed with SPSS 15.0 computer program. Results were presented as Mean ± Standard Deviation (SD). After descriptive statistics, mean caspase 3, 8 and 9 values were compared with Kruskal-Wallis Variance Analysis. Then, Mann Whitney U test followed by Bonferroni correction was used to compare the differences among the groups. A p value less than 0.05 was considered as statistically significant.

Results

Comparisons with respect to control (group A) and combination of all three drugs (group E) were presented in the tables 1 and 2.

Table 1. Caspase activity in the hippocampus (CA1 region) with respect to groups.

	Caspase-3	Caspase-8	Caspase-9
Group A	15.7±1.9	15.2±1.6	16.0±1.8
Group B	21.5±2.0*#	21.4±1.4*#	22.0±1.6*#
Group C	16.5±0.5	16.0±0.5	16.6±0.6
Group D	29.6±1.7*#§	28.3±1.0*#§	30.0±4.0*#§
Group E	19.9 ±1.6#	19.0±1.5*#	20.4±1.2*#

Data (immunoreactive cells) are expressed as Mean ± SD
Group A (control)
Group B (isoflurane)
Group C (isoflurane+dantrolene)
Group D (isoflurane+ketamine)
Group E (isoflurane+ketamine+dantrolene)
*: p< 0.05 versus (vs) group A
#:p< 0.05 vs group C
§:p<0.05 vs group E

Table 2. Caspase activity in the hippocampus (dentate gyrus region) with respect to groups.

	Caspase-3	Caspase-8	Caspase-9
Group A	18.5±2.2	16.5±1.3	18.4±1.8
Group B	24.7±0.9*#§	22.7±0.9*#	29.7±3.8*#§
Group C	19.4±1.8	18.1±1.0	19.9±1.6
Group D	34.2±1.4*#§	30.2±2.0*#§	39.3±3.1*#§
Group E	21.0±1.4	20.4±1.8	22.9±1.7*

Data (immunoreactive cells) are expressed as Mean ± SD
Group A (control)
Group B (isoflurane)
Group C (isoflurane+dantrolene)
Group D (isoflurane+ketamine)
Group E (isoflurane+ketamine+dantrolene)
*: p< 0.05 versus (vs) group A
#:p< 0.05 vs group C
§:p<0.05 vs group E

Caspase activity (3, 8 and 9) in the hippocampus CA1 region

Isoflurane alone (group B) and isoflurane+ketamine (group D) resulted in increased caspase activation (caspase 3, 8 and 9) with respect to control (group A) (p=0.004). After exposure of isoflurane+dantrolene (Group C), caspase activity did not differ from the control group which can be explained by the inhibitory effect of dantrolene on isoflurane induced caspase activation. There was an increased caspase activity in group D with respect to control. There was a decreased caspase activity in group E because of inhibitory potential of dantrolene against neuroapoptosis.

There was a markedly increased caspase activity by isoflurane+ketamine in group D which was affected by addition of dantrolene to isoflurane+ketamine in group E. After exposure of isoflurane+ketamine+dantrolene (Group E), caspase 3 activity did not show any significant difference with respect to control but caspase 8 and 9 were significantly higher with respect to control group (p=0.004) (table 1).

Caspase activity (3, 8 and 9) in the dentate gyrus region

After exposure of isoflurane (group B) and isoflurane+ketamine (group D), there was a significantly increased caspase activation (caspase 3, 8 and 9) when compared to group A.

Exposure of isoflurane (group B) and isoflurane+ketamine (group D) resulted in signicantly increased caspase activity when compared to control. Of note, group E (isoflurane+ ketamine + dantrolene) and group A (control) were similar. Caspase 3 and 9 in group B and caspase 3,8 and 9 activity in group D were inhibited by isoflurane+ketamine+dantrolene (group E) (p=0.004) (table 2).

Histopathologic findings

The immunoreactive cells in the hippocampus cross-sections indicated with black arrow were displayed (figures 1 A, B, C, D, E and F).

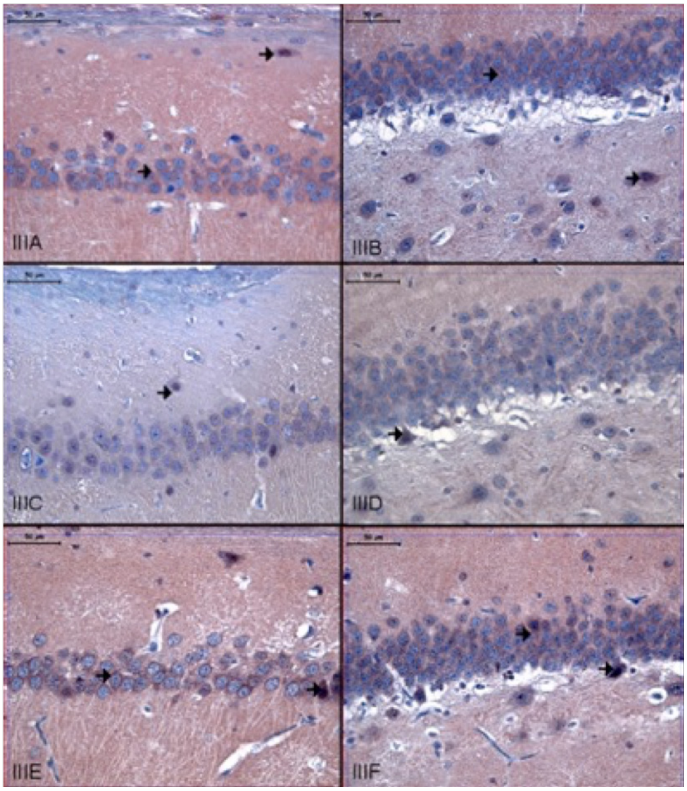

Figure 1. Caspase 3 immunoreaction in the hippocampus crossections indicated with an arrow (>). Immunoperoxidase & hematoxilen staining, magnification X 400.
(A) CA1 area in group B
(B) dentate gyrus regions in group B
(C) CA1 area in group C
(D) dentate gyrus regions in group C
(E) CA1 area in group D
(F) dentate gyrus regions in group D

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Discussion

In the present study, we demonstrated that exposure of isoflurane with or without ketamine significantly increased the caspase activity (caspase 3, 8 and 9 positive neurons) in the hippocampus where it is the major target site for general anesthetics in the central nervous system. Our current data also provided a couple of insights. First, although isoflurane and ketamine were individually known to be associated with neurodegeneration, more prominent neuroapoptotic effect was observed after exposure to isoflurane plus ketamine in terms of increased caspase activation. The reason how we designed the study groups and why we selected these anesthetics are; ketamine is an intravenous anesthetic agent used for induction of anesthesia and isoflurane is an anesthetic commonly used for maintenance of anesthesia which means these two anesthetics are used together in a consecutive manner in a standard anesthesia practice. Secondly, we might indirectly suggest that addition of dantrolene to isoflurane+ketamine could have attenuated neuroapoptosis via a potential inhibitory neuroprotective by decreasing caspase activation in the current experimental setting.

Apoptotic effect of isoflurane was investigated by detecting immunohisthochemical activity for caspase activity in rats exposed to isoflurane at different concentrations with different durations. Earlier trials reported that either a 6 h exposure of isoflurane in combination with midazolam and nitrous oxide resulted in a widespread apoptotic neurodegeneration or a 4-h administration of isoflurane as a single anesthetic agent provoked brain cell death followed by learning impairment, memory retention tests and spatial learning later in adulthood [3,4].

After exposure of 1.4% isoflurane to prefrontal cortex of 5 to 6 month-old rats for 3 times with a 2-h duration every 15 min, significantly higher caspase 3 expression than the control group was observed [9]. When isoflurane 1%, 1.5% or 2% was administered to 2 to 3-month old rats for a period of 1 h) [10], prominent neurodegeneration was encountered 3 hours after 1% isoflurane exposure in the hippocampus CA1 region of the rats. Similarly, we found a significantly increased caspase activation in the hippocampus after 2 h administration of 1.4% isoflurane with or without ketamine. In a study by Xie et al, when rats were exposed to 1.4% isoflurane in 100% O2 for 2 hours in closed cages [9], maximum immunohisthochemical activity for caspase 3 at the cerebral cortex was found after 6 hours. Therefore, we particularly evaluated the caspase activity in the hippocampal CA1 and dentate gyrus areas 6 hours after 1.4% isoflurane administration in order to find the maximum effect.

Similar to isoflurane induced apoptotic effects, ketamine caused an accelerated neurodegeneration/neuronal apoptosis and neurocognitive deficit via caspase-3 activation in newborn rats [5] Single or multiple consecutive doses of ketamine (5 mg/kg, 10 mg/kg and 20 mg/kg) were administered to 7 day-old rats subcutaneously to evaluate caspase 3 activity at frontal cortex 6 hours after anesthesia. Six consecutive doses of 5 mg/kg and 10 mg/kg ketamine and single dose or 3 consecutive doses of 20 mg/kg ketamine did not result any neurotoxic effect whereas 6 consecutive doses of 20 mg/kg ketamine elevated caspase 3 activity [11]. Based on these findings, we designed our study to use a single dose of 40 mg/kg ketamine and observed elevated caspase activity in rats treated with 1.4% isoflurane for 2 hours.

Apoptotic effect of isoflurane and ketamine were investigated in cell culture studies as well. Both isoflurane and ketamine were associated with increased caspase 3 activity [7, 12]. Our results also demonstrated neuroapoptosis with both agents; a higher degree of caspase activity with isoflurane+ketamine than isoflurane alone.

There are mainly two major biochemical pathways for caspase activation in execution of apoptosis. The intrinsic (mitochondrial) pathway of apoptosis involves mitochondrial dysfunction, release of cytochrome c and subsequent activation of caspase-9 at the apoptosm. The extrinsic (death receptor) pathway is initiated by binding of death receptors to the death ligands and subsequent recruitment of an adaptor protein and caspase-8 into the death-induced signaling complex. These pathways converge to activate effector caspase-3 which cleaves several cellular proteins leading to apoptosis involving DNA fragmentation in the nucleus. [6] Currently, we identified neuroapoptosis in the hippocampus using immunostaining for elucidating the activated suicide enzyme caspase-3 which was significantly decreased by dantrolene particularly in isoflurane+ketamine induced apoptosis.

General anesthetics produce drug-specific and distinctive effects by modulating either excitatory and/or inhibitory synaptic transmission via different pathways in the central nervous system. Gamma (γ) amnino butyric acid (GABA) is the major inhibitory neurotransmitter and the density of GABAA receptor was highest in CA1 and dentat gyrus subregions of hippocampus. Glutamate is the major excitatory neurotransmitter in the hippocampus and there are two functional subtypes as N-Methyl D-Aspartate (NMDA) and non-NMDA glutamate receptor [13]. Volatile anesthetic

isoflurane, enhances GABAA receptor activity whereas intravenous anesthetic ketamine blocks NMDA glutamate receptors [14]. We already know that neurodegeneration following exposure to isoflurane and ketamine was established in developing animals [1]. As for ketamine induced apoptosis which was found to be concentration and time dependent via mitochondrial pathway was completely prevented by caspase inhibition [15]. It was also reported that apoptosis inducing effect of ketamine is unlikely to involve NMDA receptor [16]. Thus, exposure to GABAA receptor agonist and/or NMDA receptor antagonists leading to neuronal inhibition do not necessarily result in neuroapoptosis.

Regarding dantrolene`s inhibitory effect on isoflurane induced cytotoxicity [7], it blocks Ca+2 release from sarcoplasmic reticulum to cytosol [16]. Calcium access to the cytosol activates Ca+2 dependent enzymes and induces irreversible cell damage, impairs functions of mithocondrium and endoplasmic reticulum and finally results in cellular death. Dantrolene was shown to be highly neuroprotective in 7 day-old rats with hypoxic brain damage [17]. In a cell culture study, pretreatment with 30 μM dantrolene for 30 min significantly decreased the number of isoflurane induced apoptotic cells from 17% to 7% [7]. In the current study we found that pretreatment with ip administration of dantrolene 10 mg/kg attenuated isoflurane and isoflurane plus ketamine induced apoptosis by decreasing caspase 3 activity, which is the main effector, around 24% and 35%, respectively.

Protective and neurotoxic effects of commonly used anesthetics either in ischemia-reperfusion or apoptosis settings were investigated in animal models [18,19]. After rats anesthetized with 1.4% isoflurane, ketamine or 70% nitrous oxide and fentanyl were subjected to either incomplete or near-complete ischemia induced by bilateral carotid occlusion, the brain was maintained at normothermia during 22 h long ischemia. Five days later, no difference among anesthetic agents was observed during incomplete ischemia. However, , isoflurane was found to be protective when compared with fentanyl and ketamine during near-complete ischemia with no difference between fentanyl and ketamine [18]. In a comparative study, increased number of activated caspase-3 positive neurons were identified by immunostaining in the cerebral cortex and basal ganglia of 7-day old mice with xenon or isoflurane anesthesia but exposure of both xenon and isoflurane resulted less neuroapoptosis. These results suggested that xenon could have exhibited a potential neuroprotective effect during isoflurane anesthesia [19]. Additionally, when exposed to these commonly used anesthetics, susceptibility of neurons both within the developing and adult rodent brain to neuroapoptosis was addressed. [19]

Based on the information related to complete organogenesis associated with low risk of preterm labor, the dogma related to the best timing of non-obstetric surgery during 2nd trimester has been recently revisited. Collectively, fetal brain was reported to be more vulnerable to the adverse neurodevelopmental effects of inhalation anesthetics and ketamine during the 3rd trimester [20].

Conclusion

Neurodegenerative effect of isoflurane with or without ketamine decreased after adding dantrolene in rats. Presumably, underlying mechanism is through intrinsic and/or extrinsic apoptotic pathways. Despite lack of available data supporting the selection of one anesthetic over the others and timing of surgery, these results might have important clinical implications when planning anesthesia for specific surgeries like non-obstetric surgery.

Declaration of conflict of interest

This study was granted with TUBITAK (Project Number:110S514. There is no conflict of interest.

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Turkish Journal of Clinics and Laboratory

To cite this article: Üçkan İ, Lafçı A, Göğüş N. Endovasküler prosedürlerde uygulanan anestezi yöntemlerinin intraoperatif ve postoperatif etkilerinin karşılaştırılması. Turk J Clin Lab 2020; 4: 262-269.

Orjinal Makale

Endovasküler prosedürlerde uygulanan anestezi yöntemlerinin intraoperatif ve postoperatif etkilerinin karşılaştırılması

Comparison of intraoperative and postoperative effects of anesthesia methods in endovascular procedures

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Öz

Amaç: Endovasküler girişimler; hem aort hem de periferik arterlerde ateroskleroz ve diseksiyon gibi vasküler patolojilerin tedavisinde uygulanmaktadır. Prosedür, özellikle çoklu sistemik hastalığı olan, yüksek riskli hastalarda invaziv operasyonlar ile karşılaştırıldığında, düşük risk, daha az kanama ve kan ürünü transfüzyonu ihtiyacı sağlaması açısından, daha kısa iyileşme süresi ile ilişkilidir. Çalışmamızın amacı, endovasküler prosedürlerde, anestezi yöntemi farklılıklarının intraoperatif dönemde hemodinamik etkileri, kardiyovasküler ilaç ihtiyacı, postoperatif komplikasyonlar, yoğun bakım ve hastane kalış süresi üzerine etkilerini karşılaştırmaktır.

Gereç ve Yöntemler: Bu çalışma için, Helsinki Deklarasyonuna göre yerel Etik Kurul onayı alındı (karar no:E-2193-06/09/2018). Üçüncü basamak hastanede kardiyovasküler cerrahi kliniğinde 1 Haziran 2013 ile 30 Haziran 2018 tarihleri arasında, aort ve periferik arter hastalığı için endovasküler prosedür uygulanan hastalar retrospektif olarak incelendi. Endovasküler prosedürlerin hangi anatomik bölgeye (abdominal veya torakal aorta, aorta-iliac bölge, femoro-popliteal bölge ya da infrapopliteal bölge) uygulandığı araştırıldı. Olguların demografik verileri (cinsiyet, yaş), eşlik eden hastalıkları, Amerikan Anestezistler Birliği risk sınıflaması skorları, anestezi yöntemi kaydedildi. İntraoperatif ortalama arteryel basınç, kalp atım hızı verileri kayıtlardan bulundu ve hesaplandı. İntraoperatif dönemde kardiyovasküler ilaçların kullanımı araştırıldı. Hastanede kalış süresi ve yoğun bakımda kalış süresi tespit edildi. Prosedürü takiben 30 gün içerisinde mortalite araştırıldı.

Bulgular: Çalışmaya toplam 260 hasta dahil edildi. Uygulanan endovasküler prosedürler, girişim yapılan anatomik bölgeye göre dört gruba ayrıldı: Grup-1(n=10) endovasküler aort onarımı olguları, Grup-2(n=84) aorta-iliak bölge, Grup-3(n=111) femoropopliteal bölge ve Grup-4(n=55) endovasküler girişim bölgesi infrapopliteal bölge olan olgular yer aldı. Hastalarda en sık görülen komorbiditeler hipertansiyon, diabetes mellitus ve sigara kullanımı idi. Grup-1 hastalarının tamamına genel anestezi yöntemi uygulanmışken; diğer tüm gruplara en çok uygulanan anestezi yöntemi monitörize anestezik bakım idi. Ayrıca sadece genel anestezi uygulanan Grup-1 dışındaki tüm gruplar, kendi içinde anestezi yöntemlerine göre karşılaştırıldı. Grup-2'de operasyon süresince ortalama arter basıncı ve kalp hızı; genel anestezi ile operasyona alınan hastalarda diğer gruplara göre istatistiksel olarak anlamlı olarak daha düşüktü ($p<0,001$). Grup-3 hastalarında operasyon süresince ortalama arter basıncı ve ortalama kalp hızı genel anestezi uygulanan hastalarda; monitörize anestezik bakım ile anestezi uygulanan hastalardan istatistiksel olarak anlamlı derecede düşüktü ($p<0,001$). Grup-4 hastalarda operasyon süresince ortalama arter basıncı; genel anestezi uygulanan hastalarda ve spinal anestezi uygulanan hastalarda; monitörize anestezik bakım ile anestezi uygulanan hastalara göre anlamlı derecede düşüktü ($p<0,001$). Grup-2 ve Grup-3' de inotrop ajan kullanımı sadece genel anestezi uygulanan hastalarda gözlendi (%16,7 ve %25). Grup-2 ve 3'te genel anestezi alan hastaların yoğun bakım ve hastane kalış süresi diğer gruplardan anlamlı düzeyde uzundu ($p<0,001$). Grup-4'de hastane kalış süresi, genel anestezi uygulanan hastalarda, diğer anestezi uygulananlara göre daha uzun idi.

Sonuç: Endovasküler girişimler için uygulanan anestezi yöntemlerini incelendiğimiz çalışmamızda; periferik arteriyel girişim yapılan, çoklu komorbiditeye sahip hastalarda, monitörize anestezik bakım yönteminin, intraoperatif stabil hemodinaminin sağlanmasında, postoperatif komplikasyonların azaltılmasında ve daha kısa yoğun bakım/ hastane yatış süreleri sağlanmasında etkili olduğunu tespit ettik.

Anahtar Kelimeler: Endovasküler prosedür; genel anestezi; spinal anestezi; monitörize anestezik bakım

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Doi: 10.18663/tjcl.780998

Abstract

Aim: Endovascular interventions are applied in the treatment of vascular pathologies such as atherosclerosis and dissection in both aorta and peripheral arteries. In comparison to invasive surgery, the procedure is associated with a lower risk, less bleeding and shorter recovery time, especially in high-risk patients with multiple systemic diseases, due to less bleeding and the need for transfusion of blood products. The aim of our study is to compare the effects of differences in anesthesia method on hemodynamic effects, cardiovascular drug need, postoperative complications, intensive care and hospital stay in endovascular procedures.

Material and Methods: Local Ethics Committee approval was obtained for this study according to the Declaration of Helsinki (decision number: E-2193-06 / 09/2018). Patients who underwent endovascular procedures for aortic and peripheral artery disease between June 1, 2013 and June 30, 2018 in a cardiovascular surgery clinic at a tertiary hospital were retrospectively analyzed. It was investigated in which anatomical region the endovascular procedures were performed (abdominal or thoracic aorta, aorta-iliac region, femoro-popliteal region or infrapopliteal region). Demographic data (gender, age) of the cases, comorbidities, American Society of Anesthesiologists risk classification scores, and anesthesia method were recorded. Intraoperative mean arterial pressure and heart rate data were found from the records and calculated. The use of cardiovascular drug in the intraoperative period was detected. The length of stay in the hospital and the duration of the intensive care unit were determined. Mortality was investigated within 30 days following the procedure.

Results: A total of 260 patients were included in the study. The endovascular procedures performed were divided into four groups according to the anatomic region where the intervention was performed: Group-1 (n = 10) endovascular aortic repair cases, Group-2 (n = 84) aorta-iliac region, Group-3 (n = 111) femoropopliteal region and Group-4 (n = 55) infrapopliteal region. The most common comorbidities in patients were hypertension, diabetes mellitus and smoking. The general anesthesia was applied to all patients in group-1, while the most common anesthesia method used in all other groups was monitored anesthetic care. Secondly, all groups except Group-1 (only under general anesthesia) were compared according to anesthesia methods within themselves. In group-2, mean arterial pressure and heart rate during the operation were statistically significantly lower in patients who were operated under general anesthesia compared to the other groups.(p‹0,001) In group-3 patients, mean arterial pressure and mean heart rate during the operation were statistically significantly lower in patients who received general anesthesia compared to patients who received monitored anesthetic care (P<0.001). The mean arterial pressure in group-4 patients during the operation was significantly lower in those who received general anesthesia and spinal anesthesia compared to patients who received monitored anesthetic care (P<0.001). Inotropic drug use in Group-2 and Group-3 was observed only in patients undergoing general anesthesia (16.7% and 25%). In the patients who underwent general anesthesia in group-2 and 3, the duration of intensive care unit and hospital stay was significantly longer than the other groups (P<0.001).In group-4, hospital stay was longer in patients who underwent general anesthesia compared to those who received other anesthesia.

Conclusion: The monitored anesthetic care method provides stable intraoperative hemodynamics, reducing postoperative complications, shorten intensive care and hospital stayin patients with multiple comorbidities undergoing peripheral arterial intervention.

Keywords: Endovascular procedure; general anesthesia; spinal anesthesia; monitored anesthetic care

Giriş

Endovasküler onarımlar, hem aort hem de periferik arterlerde artan sıklıkta ve başarı ile uygulanmaktadır. Endovasküler aortik ve periferik arteriyel rekonstrüksiyonlar laparotomi, geniş cerrahi kesi ve vasküler klempleme ihtiyacını ortadan kaldırır. Böylece açık cerrahilerin aksine, düşük risk, daha az kanama ve daha az kan ürünü transfüzyonu ihtiyacı, daha kısa iyileşme süresi ile öne çıkmaktadır.[1] Amerikan Kardiyoloji Koleji ve Amerikan Kalp Derneği (ACC/AHA) kılavuzları da endovasküler prosedürleri orta riskli bir prosedür olarak kabul etmektedir. Fakat bu girişimler, çoğunlukla ileri yaş ve çoklu komorbiditesi olan, yüksek Amerikan Anestezistler Birliği (ASA) risk grubuna sahip hastalara uygulanmaktadır.[2]

İntraoperatif anestezik yönetim için ana hedefler, intravasküler volümün korunması, kanamanın erken teşhisi ile hemodinamik stabilitenin sağlanması, beyin, kalp, omurilik, böbrek ve splanknik bölge gibi hayati organ perfüzyonunu korunması, miyokardiyal oksijen ihtiyacının karşılanması, ve normoterminin sürdürülmesidir. Bu olgularda lokal infiltrasyon anestezisi, monitörize anestezik bakım (MAC), rejyonel veya genel anestezi (GA) uygulanabilir. Ancak bu yöntemlerin herhangi birinin diğerine göre üstünlüğü; intraoperatif veriler ve postoperatif komplikasyonlar bakımından açıkça ortaya konamamıştır.[3]

Bu çalışmada, endovasküler prosedürlerde uygulanan farklı anestezi tekniklerini, intraoperatif hemodinamik durum ve kardiyovasküler ilaç ihtiyacı, postoperatif hasta sonuçları bakımından karşılaştırmayı amaçladık.

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Gereç ve Yöntemler

Bu çalışma, Helsinki Deklarasyonuna göre yerel Etik Kurul tarafından değerlendirilerek onaylandı (karar no:E-2193-06/09/2018). Üçüncü basamak hastanede kardiyovasküler cerrahi kliniğinde 1 Haziran 2013 ile 30 Haziran 2018 tarihleri arasında, aort ve periferik arter hastalığı için endovasküler prosedür uygulanan hastalarda, hastane kayıtları retrospektif olarak incelendi. Açık cerrahi prosedür yapılmış olgular çalışma dışı bırakıldı. Endovasküler prosedürlerin hangi anatomik bölgeye (abdominal veya torakal aorta, aorta-iliak bölge, femoro-popliteal bölge ya da infrapopliteal bölge) uygulandığı tespit edildi. Tüm hastalarda elektrokardiyografi, ortalama arteryel basınç, periferik oksijen satürasyonunu içeren monitorizasyon uygulandı. GA için indüksiyonda midazolam (1-2 mg), propofol (1-2 mg/kg), fentanil (2-4 µg/kg) ve roküronyum (0,6 mg/kg) kullanılarak endotrakeal entübasyon yapıldı. İdame sevofluran ve O2–hava karışımı ile sağlandı. Spinal anestezi (SA), tek doz bupivakain ile L3-4 veya L4-5 seviyesinden uygulandı. MAC için midazolam (0,01-0,1mg/kg) ve remifentanil (1.0 mcg/kg) ile sedasyon sağlandıktan sonra cerrah tarafından girişim bölgesine infiltrasyon bloğu yapıldı.

Olguların demografik verileri (cinsiyet, yaş), eşlik eden hastalıkları, ASA risk sınıflaması skorları incelendi. Uygulanan anestezi yöntemi kaydedildi. İntraoperatif ortalama arteryel basınç ve kalp atım hızı verileri kayıtlardan bulundu ve hesaplandı. İşlem sırasındaki bradikardi (kalp hızının 50 atım/dk altına düşmesi), taşikardi (kalp hızının 110 atım/dk üzerine çıkması), hipotansiyon (başlangıca göre %30'dan fazla düşüş veya sistolik kan basıncının 90 mmHg'nın altına düşmesi) ve hipertansiyon (başlangıca göre %30'dan fazla artış veya sistolik kan basıncının 159 mmHg'nın üstüne çıkması) gibi hemodinamik değişiklikler kaydedildi. İntraoperatif dönemde kardiyovasküler ilaçların (noradrenalin, dopamin ya da nitrogliserin) kullanım verileri kaydedildi. Postoperatif dönemde gelişen pulmoner, kardiyovasküler, nörolojik ve renal komplikasyonlar kaydedildi. Hastanede kalış süresi ve yoğun bakımda kalış süresi tespit edildi. Prosedürü takiben 30 günlük mortalite araştırıldı.

İstatistiksel analiz

Çalışmadan edinilen bulguların değerlendirilmesinde SPSS 22 programı istatiksel analizi kullanıldı. Nicel değişkenleri dört grupta karşılaştırırken değişkenlerin her grupta normal dağılıp dağılmadığını Shapiro-Wilk testi ile incelendi. Normal dağılım varsayımı sağlanmadığı durumlarda gruplar Kruskal-Wallis testi ile karşılaştırıldı. İstatiksel açıdan anlamlı fark bulunmadığında ikili karşılaştırmalar Dunn düzeltmesi ile yapıldı. Nitel değişkenler açısından karşılaştırma yapılırken Pearson Ki-kare testi yapıldı. Veriler özetlenirken nicel değişkenler için ortanca (min-max), nitel değişkenler için frekans (yüzde) raporlandı. Her iki yönlü P değeri ≤%5 istatiksel açıdan anlamlı kabul edildi.

Bulgular

Çalışmaya toplam 260 hasta dahil edildi. Uygulanan endovasküler prosedürler, girişim yapılan anatomik bölgeye göre dört gruba ayrıldı: Grup-1'de(n=10) abdominal veya torakal aort anevrizması veya rüptürü için yapılan EVAR-TEVAR olguları, Grup-2'de(n=84) endovasküler girişim bölgesi aorta-iliak bölge olan olgular, Grup-3(n=111) de endovasküler girişim bölgesi femoropopliteal bölge olan olgular ve Grup-4(n=55) de endovasküler girişim bölgesi infrapopliteal bölge olan olgular yer aldı. Tüm gruplarda hastaların çoğunluğu erkek cinsiyet idi. En genç hasta 27 yaşında ve Grup-1 de, en yaşlı iki hasta ise 84 yaşında ve Grup-1 ve Grup -3 de idi. En sık görülen komorbid durumlar sırasıyla hipertansiyon(HT), diabetes mellitus (DM) ve sigara kullanımı idi (Tablo-1). Grup-1 hastalara sadece genel anestezi yöntemi uygulanırken; diğer gruplara MAC (en sık), GA ve SA anestezi yöntemleri uygulandı (Tablo-2). Operasyon süresince ortalama arteryel basınç (OAB); Grup-1'de en düşük iken, ortalama kalp hızı Grup-1 ve Grup-4'de en düşük olduğu görüldü. İnotrop ilaç kullanımı en fazla Grup-1'de iken, Grup-4'de hiçbir hastanın inotrop ilaç ihtiyacı olmadı (Tablo-3).

Sadece genel anestezi uygulanan Grup-1 dışındaki tüm gruplar, kendi içinde anestezi yöntemlerine göre karşılaştırıldığında elde edilen veriler değerlendirildi (Tablo-4). Grup-2'de operasyon süresince OAB; GA ve MAC uygulananlar karşılaştırıldığında, genel anestezi ile operasyona alınan hastalarda istatistiksel olarak anlamlı derecede daha düşüktü(P<0.001). SA ve MAC arasında da istatistiksel anlamlı fark vardı(P=0.009). Operasyon süresince ortalama kalp hızı ise GA uygulanan hastalarda MAC uygulananlardan anlamlı derecede düşüktü (P<0.001). Grup-3 hastalarında operasyon süresince OAB ve ortalama kalp hızı GA uygulanan hastalarda; MAC ile anestezi uygulanan hastalardan istatistiksel olarak anlamlı derecede düşüktü (P<0.001). Grup-4 hastalarda operasyon süresince OAB; GA uygulanan hastalarda ve SA uygulanan hastalarda; MAC ile anestezi uygulanan hastalara göre anlamlı derecede düşüktü (P<0.001). Bu grupta intraoperatif ortalama kalp hızı, her üç anestezi yöntemi uygulanan hastalarda benzer idi.

Grup-2 ve Grup-3' de inotrop ajan kullanımı sadece GA uygulanan hastalarda gözlendi (%16,7 ve %25) Grup-4' de antihipertansif ajan kullanımı; MAC uygulanan hastalarda,

Tablo 1. Hasta karakteristikleri

		Grup 1 (n=10)	Grup 2 (n=84)	Grup 3 (n=111)	Grup 4 (n=55)
Yaş		61.10±18.61 65.5 (27-84)	65.61±8.88 65 (48-80)	61.69±7.67 62 (46-84)	58.69±8.89 56 (50-74)
Cinsiyet	Erkek	7 (%70)	82 (%97.6)	103 (%92.8)	54 (%98.2)
	Kadın	3 (%30)	2 (%2.4)	8 (%7.2)	1 (%1.8)
ASA	ASA2	2 (%20)	39 (%46.4)	61 (%55)	41(%74.5)
	ASA2E	1 (%10)	1 (%1.2)	0 (%0)	0 (%0)
	ASA3	5 (%50)	42 (%50)	48 (%43.2)	14(%25.5)
	ASA3E	1 (%10)	1 (%1.2)	2 (%1.8)	0 (%0)
	ASA4	0 (%0)	1 (%1.2)	0 (%0)	0 (%0)
	ASA4E	1 (%10)	0 (%0)	0 (%0)	0 (%0)
Komorbiditeler	Sigara	4 (%40)	34 (%40.5)	75 (%67.6)	35 (%63.6)
	HT	6 (%60)	77 (%91.7)	86 (%77.5)	38 (%69.1)
	DM	5 (%50)	43 (%51.2)	68 (%61.3)	27 (%49.1)
	Nörolojik hastalık	2 (%20)	1 (%1.2)	20 (%18.0)	2 (%3.6)
	Renal hastalık	3 (%30)	1 (%1.2)	5 (%4.5)	1 (%1.8)
	Kardiyak hastalık	5 (%50)	40 (%47.6)	21 (%18.9)	11 (%20)
	Respiratuar hastalık	1 (%10)	16 (%19)	4 (%3.6)	2 (%3.6)

Grup1: Abdominal veya torakal aort anevrizması veya rüptürü için yapılan EVAR-TEVAR olguları; Grup 2: Endovasküler girişim bölgesi aorta-iliak bölge olan olgular;Grup 3: Endovasküler girişim bölgesi femoropopliteal bölge olan olgular; Grup4:Endovasküler girişim bölgesi infrapopliteal bölgeolan olgular.ASA:American Society of Anesthesiologists. Değerler ortalama±Standart sapma, medyan, minimum-maksimum ve sayı (%) olarak verilmiştir

Tablo 2. Uygulanan anestezi yöntemlerinin gruplara göre dağılımı

	Grup 1 (n=10)	Grup 2 (n=84)	Grup 3 (n=111)	Grup 4 (n=55)
Genel anestezi	10 (100)	6 (7.1)	20 (18)	4 (7.3)
Spinal anestezi	0(0)	3 (3.6)	6 (5.4)	8 (14.5)
Monitörize anestezik bakım	0(0)	75 (89.3)	85 (76.6)	43 (78.2)

Değerler sayı (%) olarak verilmiştir

Tablo 3. İntraoperatif dönemde ortalama arter basıncı, kalp hızı, inotrop ve antihipertansif ihtiyacı

	Grup 1 (n=10)	Grup 2 (n=84)	Grup 3 (n=111)	Grup 4 (n=55)
Ortalama arter basıncı	63 (55-72)	90(60-101)	85(60-99)	80(55-100)
Kalp hızı	68 (65-84)	88(60-110)	82(65-110)	75(70-90)
İnotrop ajan gereksinimi	4 (%40)	1 (%1.2)	5 (%4.5)	0 (%0)
Antihipertansif ilaç gereksinimi	0 (%0)	2 (%2.4)	3 (%2.7)	9 (%16.4)

Değerler sayı (%) olarak verilmiştir

Tablo 4. İntraoperatif ortalama arteriyel basınç ve kalp hızının anestezi yöntemlerine göre karşılaştırması

		GA	SA	MAC	P value
	Ortalama arter basıncı	64.00±5.79 63(55-72)			
	Kalp hızı	71.20±6.64 68(65-84)	-	-	-
	Ortalama arter basıncı	64.00±4.94 62.5 (60-72)	81.33±3.21 80(79-85)	93.55±4.48 90(90-101)	*P<0.001 **P=0.009
	Kalp hızı	70.00±6.75 71.5 (60-77)	80.00±5.00 80(75-85)	87.29±7.14 90(75-110)	*P<0.001 **P=0.100
	Ortalama arter basıncı	66.85±5.82 66(60-80)	81.50±4.13 80(77-88)	89.68±9.34 90 (75-99)	*P<0.001 **P=0.100
	Kalp hızı	70.80±5.60 68(65-81)	82.17±4.70 82.5(75-88)	90.75±8.56 95.00(80-110)	*P<0.001 **P=0.10
	Ortalama arter basıncı	64.50±6.40 67.00 (55-69)	76.50±4.34 78.00(67-80)	89.09±8.58 90.00(80-100)	*P<0.001 **P<0.001
	Kalp hızı	76.50±5.80 76 (70-84)	80.13±4.76 80(75-88)	78.84±5.43 75 (75-90)	*P=0.100 **P=0.100

Değerler ortalama±Standart sapma, medyan ve minimum-maksimum olarak verilmiştir; OAB:Ortalama arteryel basınç; GA:Genel anestezi, SA: Spinal anestezi, MAC:monitörize anestezik bakım. *GA ve MAC karşılaştırması, **SA ve MAC karşılaştırması.

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diğer anestezi yöntemi uygulanan hastalardan daha fazlaydı (%18,6). Grup-2 ve 3'de yoğun bakım kalış süresi açısından GA ve MAC uygulananlar arasında istatistiksel anlamlı fark vardı(P<0.001). GA alan hastaların yoğun bakım kalış süresi diğerlerinden anlamlı düzeyde uzundu (P<0.001). Hastane kalış süresi de aynı şekilde GA uygulananlarda daha uzundu. SA uygulananlarda hem yoğun bakım hem de hastane kalış süresi MAC ile anlamlı farklı değildi. Grup-4 hastalarda yoğun bakımda kalış süresi GA uygulananlarda daha uzundu; ancak bu fark anlamlı değildi. Hastane kalış süresi, GA uygulanan hastalarda, MAC uygulananlara göre istatistiksel olarak anlamlı düzeyde uzundu (p=0,035) (Tablo 5).

Grup-2 ve 3 de nörolojik komplikasyon sadece birer hastada rastlandı ve bu hastaların anestezi uygulaması GA idi. Renal komplikasyonlar; hastane yatış süreleri uzayan hastalarda gözlenen en sık komplikasyondu. Diğer uzamış hastane yatış süreleri ise pulmoner ve kardiyak nedenler ile ilgili idi. Hastaların sadece 4'ünde pulmoner komplikasyon izlendi. Dört hastanın da anestezi şekli GA idi. Kardiyak komplikasyon en fazla Grup-1'de ve Grup 3' de idi. Grup-1'de önceden bilinen kardiyak hastalığı olmayan 5 hastanın 2'sinde kardiyak komplikasyon(aritmi, kalp yetmezliği) tespit edildi. Grup-3 ve 4'de kardiyak komplikasyon, GA uygulanan hastalarda daha fazla idi. İlk 30 günde mortalite sadece iki hastada gözlendi ve her iki hasta da Grup-1 içerisinde yer alıyordu ve GA uygulandı. Mortalite gelişen bu iki hastada respiratuar ve kardiyak komplikasyon meydana geldi (Tablo 6)

Tablo 5. Yoğun bakım ünitesinde kalış süresi ve hastanede kalış süresinin anestezi yöntemlerine göre karşılaştırması

		GA	SA	MAC	P Value
Grup 1	YBÜ kalış süresi (saat)	84.00±138.21 12 (0-408)	-	-	-
	Hastane kalış süresi (gün)	12.40±11.75 9 (1-35)	-	-	-
Grup 2	YBÜ kalış süresi (saat)	4.00±1.94 0 (0-6)	2.00±3.46 0 (0-6)	1.00±2.44 0 (0-6)	*P<0.001 **P=0.100
	Hastane kalış süresi (gün)	12±21.10 4 (1-55)	2.67 ± 1.15 2(2-4)	2.72±0.89 3 (0-4)	*P<0.001 **P=0.100
Grup 3	YBÜ kalış süresi (saat)	10.55±32.27 0 (0-144)	1.67±2.65 0 (0-6)	3.09±2.54 3 (0-10)	*P<0.001 **P=0.100
	Hastane kalış süresi (gün)	4.75±2.33 4.5 (2-11)	3.17±0.75 3 (2-4)	2.56±1.67 2 (0-5)	*P<0.001 **P=0.100
Grup 4	YBÜ kalış süresi (saat)	3.28±2.08 0 (0-6)	1.75±3.05 0 (0-8)	1.50±3.00 0 (0-6)	*P=0.100 **P=0.100
	Hastane kalış süresi (gün)	8.50±9.84 5 (1-23)	3.25±0.88 3 (2-5)	2.93±0.25 3 (2-3)	*p= 0.035 **P=0.100

Değerler ortalama±Standart sapma, medyan ve minimum-maksimum olarak verilmiştir; OAB:Ortalama arteryel basınç; GA:Genel anestezi, SA: Spinal anestezi, MAC:monitörize anestezik bakım. *GA ve MAC karşılaştırması, **SA ve MAC karşılaştırması.

Tablo 6. Grupların postoperatif komplikasyonlar yönünden incelenmesi

	Grup-1	Grup-2	Grup-3	Grup-4
Nörolojik komplikasyonlar	0 (%0)	1 (%1.2)	1 (%0.9)	0 (%0)
Renal komplikasyonlar	4 (%40)	2 (%2.4)	4 (%3.6)	1 (%1.8)
Pulmoner komplikasyonlar	3 (%30)	0 (%0)	1 (%0.9)	0 (%0)
Kardiyak komplikasyonlar	2 (%20)	0 (%0)	16 (%14.4)	7 (%12.7)

Değerler sayı (%) olarak verilmiştir

Tartışma

Bu çalışmada, endovasküler periferik arter girişimlerinde monitörize anestezik bakım yönteminin intraoperatif stabil hemodinaminin sağlanmasında etkili olduğu, postoperatif komplikasyonları azalttığı ve hastane yatış sürelerini kısalttığı tespit edildi. Endovasküler arteriyel girişimler torakal, abdominal aort veya periferik arterleri içerebilir. Bu girişimlerde hastanın komorbiditeleri ve primer patolojisi önemlidir. Endovasküler aort anevrizması onarımı, konvansiyonel açık prosedürlerle karşılaştırıldığında, daha düşük perioperatif mortalite ve morbidite ile ilişkilidir. Ayrıca perioperatif komplikasyonların ve mortalitenin azaltılması için anestezik yönetim önemlidir. Fakat anestezi yöntemi intraoperatif ve postoperatif sürecin tek belirleyicisi değildir. Anestezi tekniği; hastaya ve yapılacak işleme uygun, hızlı derlenme sağlayacak şekilde planlanmalı, hasta sonuçları üzerine olumlu etkileri olmalıdır.

EVAR uygulamalarında hangi tip anestezinin en uygun olduğu ise hala cevaplanması gereken bir sorudur.[4] Kılavuzlarda, EVAR uygulamaları için MAC yöntemi ön plana çıkmaktadır.[5] Fakat pek çok merkezde EVAR, çalışmamızda olduğu gibi en sık genel anestezi altında uygulanmaktadır. Bulut ve ark tarafından yapılan açık ve endovasküler aort onarımlarının karşılaştırıldığı bir çalışmada endovasküler girişimler de genel anestezi altında yapılmıştır.[6] Gümüş ve ark. yaptığı benzer çalışmada da EVAR için çoğunlukla genel anestezi tercih edildiği görülmektedir.[7] Bu prosedürlerde anestezi yöntemi; hastanın ve anestezi uzmanının tercihi, cerrahi ekibin deneyimi, anevrizmanın karmaşıklığı ve hastanın komorbiditeleri, kullandığı ilaçlar dikkate alınarak karar verilmelidir. Endovasküler onarım süresinin uzun olduğu durumlarda sadece lokal anestezi uygulaması, hasta konforu yanında işlemin başarısı için gerekli olan tam bir hareketsizlik durumunun sağlanmasında yetersiz kalabilir. Bizim uygulamalarımızda da, açık operasyona dönme ihtimali ve cerrahi ekibin de tam hareketsizlik talep etmesi nedeniyle EVAR olguları genel anestezi altında işleme alındı. Torakal ve/veya abdominal aortaya stent greft yerleştirilen hastalarda, bu şekilde hemodinamik stabilite ve kontrollü solunum ile greftin optimal lokasyonu sağlanabildi.

Yapılan çalışmaların çoğunda anestezik yöntemlerin mortalite üzerine etkisinin olmadığı gösterilmiştir.[8,9] Holt ve ark. yaptığı bir çalışmaya göre elektif EVAR sonrası 30 günlük mortalite %1-2'dir.[10] Postoperatif dönemde iki hastamızda, ilk 30 gün içinde mortalite meydana geldi. Bunun nedeni ölen hastaların Tip III diseksiyon nedeniyle acil girişim yapılmış olgular olması mortalitede etkili olabileceğini düşünmekteyiz. Çünkü bu olgulardaki yüksek mortalite, anestezik yöntemden bağımsız olarak rüptür ya da açık operasyona dönme zorunluluğu nedeniyle olmaktadır. Ayrıca intraoperatif diseksiyon ve kanama gibi mortal komplikasyonlar, kontrolsüz intraoperatif hipertansiyon nedeniyle de meydana gelebilir.

Günümüzde endovasküler revaskülarizasyon, aortoiliak oklüzif hastalıklar için de, öncelikli yaklaşım haline gelmektedir.[11] Buna rağmen periferik endovasküler revaskülarizasyon olgularında anestezi yönetimi EVAR kadar incelenmemiştir. Tüm alt ekstremite vasküler girişimlerde (Grup-2,3,4) başarılı sonuçlar için risk faktörlerinin belirlenmesi, uygun cerrahi ve anestezi yönetiminin tanımlanması gereklidir.[12] Çalışmamızda yer alan tüm gruplarda olduğu gibi bu grup hastalıklarda çoğunlukla ileri yaş, erkek cinsiyet ve kronik obstrüktif akciğer hastalığı (KOAH) nedeniyle yüksek ASA skoruna sahip olma, hipertansiyon, DM ve sigara kullanımı en sık gözlenen komorbidite faktörleridir. Ayrıca tıkayıcı periferik arter hastalıklarına sıklıkla aterosklerotik kalp hastalığı da eşlik etmektedir. Bu hastalarda anestezi tekniği, önemli hemodinamik değişiklikler oluşturabilir. Şimdiye kadarki çalışmalar genellikle anestezi tekniğinin etkilerinin özellikle postoperatif dönemdeki sonuçlar (yoğun bakım ve hastanede kalış süresi, sistemik komplikasyonlar, mortalite) üzerinden araştırmışlardır.[3,13,14] Anestezi yönteminin perioperatif hemodinami, inotropik-antihipertansif tedavi ve postoperatif komplikasyon gelişimi üzerine etkileri ile ilgili bilgiler azdır. Bu konuda yapılan çalışmalardan; Bettex ve ark. daha az vazopressör ilaç gereksinimi ve daha az pozitif sıvı dengesi sağlaması nedeniyle MAC'ın, GA ve rejyonel anesteziye üstünlükleri olduğunu vurgulamışlardır.[15] Bizim çalışmamızda da Grup-2,3 ve 4 için MAC, en fazla tercih edilen anestezi yöntemi oldu. Böylece her 3 grupta da intraoperatif kararlı hemodinami sürdürülmesi ve inotrop ilaç ihtiyacının azalma sağlanmıştır. MAC uygulanan hastaların %90'nında intraoperatif vasopressör ilaç ihtiyacı olmadı.

Endovasküler prosedür uygulanan hastalar, postoperatif dönemde greft bölgesinden kaynaklanan problemler ya da perioperatif sıvı tedavisindeki dengesizlikler nedeniyle akut böbrek hasarı için yüksek risk altındadır. İntravenöz kontrast madde kullanımı, ileri yaş ve çoklu komorbiditeler, perioperatif dehidrasyon, perioperatif dönemde kullanılan ACE inhibitörleri, diüretiklerin kullanımı renal komplikasyonlar ile ilişkilidir.[16,17] Ayrıca anestezik ilaçlar da böbrek fonksiyon bozukluğuna katkıda bulunabilir.[18] Uygun anestezik yöntemin seçiminin yanısıra, yeterli hidrasyonun sağlanması, kontrast yükünün sınırlandırılması ve nefrotoksik ilaç kullanımının azaltılması gibi önlemlerle böbrek yetmezliği gelişimi en aza indirilebilir.[19] Çalışmamızda anestezik ilaç kullanımının en aza indirildiği MAC hastalarında renal komplikasyonlar daha az iken, genel anestezi uygulanan ve renal artere yakın girişim uygulanan EVAR hastalarında renal komplikasyonlar daha fazla idi.

Lumsden ve arkadaşları; erken postoperatif ambulasyonla, hareketsiz hastalarda oluşan pulmoner komplikasyonların azaltılabileceği ve vasküler greftlerde stazın önlenebileceğini savunmuşlardır.[20] Boulos ve arkadaşları aortailiak hastalık nedeniyle endovasküler prosedür uygulanan 3110 hastayı retrospektif olarak incelediler. Çalışma sonucunda, MAC uygulanan hastalarda, postoperatif pulmoner komplikasyonlar olarak uzamış mekanik ventilasyon ve yeniden entübasyonu GA uygulananlara göre daha az gözlemlediler. MAC grubunda

hastane kalış süresi de anlamlı olarak daha kısa idi.[21] Edwards ve arkadaşları; Amerikan Cerrah Koleji Ulusal Cerrahi Kalite Geliştirme Programı veritabanını kullanarak retrospektif olarak elektif vasküler rekonstrüksiyon geçiren hastaları inceledikleri çalışmalarında, lokal anestezi, MAC ve spinal anestezi kullanımının, genel anesteziye kıyasla pulmoner komplikasyonlarda anlamlı bir azalma ile ilişkili olduğunu göstermiştir.[9] Spinal anestezi ve MAC ile aynı zamanda hastane kalış süresinin azaldığını gözlemlemişlerdir. Aynı şekilde Fereydooni ve arkadaşları; yine aynı geliştirme programı verilerine dayanarak alt ekstremite revaskularizasyonlarında spinal ve epidural anestezi kullanımını incelemişler. Spinal ve epidural anestezi kullanımın hastane kalış ve perioperatif morbidite azalttığı sonucuna varmışlardır.[22] Bizim çalışmamızda da postoperatif pulmoner komplikasyon gelişimi, genel anestezi alan hastalarda diğer gruplara göre daha fazla idi. Periferik endovasküler prosedürlerde MAC uygulaması ile pulmoner komplikasyonlarda azalmaya bağlı erken mobilizasyonun da sağlandığını düşünmekteyiz. Bu sayede hastane yatış süresi, MAC uygulananlarda daha kısa bulundu.

Bu çalışmanın retrospektif olması nedeniyle bazı kısıtlamaları mevcuttur. Tarafsızlık tam anlamıyla sağlanamamıştır. Kliniğimizde kardiyovasküler cerrahi ekibi ve sorumlu anestezi ekibi sabit olmasına rağmen, endovasküler prosedürlerin uygulandığı vakalarda, hasta ve cerrahi konfor kaygısı anestezi yöntemi tercihimizi etkilemiştir. Endovasküler aort tamiri sadece genel anestezi ile yapılabilmiştir, diğer anestezi yöntemleri ile karşılaştırma imkanımız olmamıştır.

Sonuç

Periferik arteriyel endovasküler girişimlerde monitörize anestezik bakım yöntemi hemodinamik stabilite sağlamasının yanısıra komplikasyonları azaltır ve hastane yatış süresini kısaltır. Bununla birlikte endovasküler girişim yapılan hastalarda anestezi yöntemi, hasta sonuçlarında primer belirleyici faktör değildir. Hastanın primer patolojisi ve eşlik eden hastalıkları da hasta sonuçlarında önemlidir.

Çıkar çatışması / finansal destek beyanı

Bu yazıdaki yazarların herhangi bir çıkar çatışması yoktur. Yazının herhangi bir finansal desteği yoktur.

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To cite this article: Özden S, Turan UF, Katar MK, Temiz A, Er S. Hartmann kolostomi kapatıldıktan sonraki klinik seyir. Turk J Clin Lab 2020; 4: 270-273.

Orjinal Makale

Hartmann kolostomi kapatıldıktan sonraki klinik seyir

Clinical course after Hartman colostomy closure

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Öz

Amaç: Amacımız, Hartmann kolostomi kapatılan hastaların klinik seyirlerindeki olumsuz etmenleri değerlendirmekti.

Gereç ve Yöntemler: 1 Ocak 2012-31 Aralık 2017 tarihleri arasında kliniğimizde Hartmann kolostomi kapatılan 66 hastanın demografik verileri, kolostomi açılma nedenleri, postoperatif yatış süreleri, yoğun bakım ihtiyacı, mortalite/morbidite varlığı, Amerikan Anesteziyoloji Derneği Skoru(ASA) ve komplikasyonları tanı/tedavi yaklaşımları ile ilgili veriler retrospektif olarak elektronik ortamdaki kayıtlarından elde edildi.

Bulgular: 66 hastanın 46(%69)'sı erkek ve 20(%31)'si kadındı. Bunların medyan yaşları 54(18-85) idi. Çalışmaya dahil olan hastaların 21(%32)'i kolorektal kanser, 11(%17)'i sigmoid volvulus, 4(%6)'ü divertikülit perforasyonu ve geri kalan 30(%45) hasta diğer nedenlerle (12 hasta sigmoid volvulus, 2 hasta yüksek enerjili patlama ve 2 hasta iskemik kolit v.b.) Hartmann kolostomi açılmış hastalardı. Ostomilerin ortalama kapatma süreleri 4±3 aydı. ASA skoru 19(%28) hastada II ve 47(%72) hastada III'dü. 19(%28) hastada cerrahi alan enfeksiyonu ve 4(%6) hastada anastomoz kaçağı tespit edildi. Kaçak tespit edilen 1(%1,5) hastada postoparatif ilk 7 günde mortalite gelişti. Mortalite gelişen hastanın Charlson Comorbidity Index (CCI)'i 6 ve ölüm nedeni de pulmoner emboliydi. 6(%9) hastada postoperatif erken dönemde (ilk 7 gün) ileus gelişti. 7(%10) hastada postoperatif yoğun bakım ihtiyacı oldu. Hastaların postoperatif yatış süreleri ortalama±SD=15,11±9,12 gündü.

Sonuç: Stoma kapanmasından sonraki morbidite ve mortalite önemsiz bir durum değildir. Hartmann prosedüründen sonra optimal kapatma intervali, uygun hasta seçimi, hastanın komorbidite yükü, merkezde yoğun bakım varlığı ve özelleşmiş veya deneyimli merkezlerde kapatılma işleminin yapılmasının uygun olacağını düşünmekteyiz.

Anahtar kelimeler: Hartmann prosedürü; komplikasyon; hartmann kolostomi kapatılması

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Doi: 10.18663/tjcl.774064

Volume 11 Number 4 p: 270-273

Abstract

Aim: Our aim was to evaluate the adverse effects of clinical course of patients with Hartmann colostomy closure.

Material and methods: Demographic data of 66 patients who had closed Hartmann colostomy at our clinic between January 1, 2012 and December 31, 2017, American Anesthesiology Association Score (ASA) and its complications / diagnosis and treatment approaches were retrospectively obtained from the electronic records.

Results: Of the 66 patients, 46 (69%) were male and 20 (31%) were female. Their median age was 54 (18-85). 21 (32%) of the patients included colorectal cancer, 11 (17%) sigmoid volvulus, 4 (6%) diverticulitis perforation, and the remaining 30 (45%) patients for other reasons (12 patients sigmoid volvulus, 2 patients had high energy burst and 2 patients had ischemic colitis, etc. Hartmann colostomy was opened. The mean closure time of the ostomies was 4 ± 3 months. The ASA score was II in 19 (28%) and III in 47 (72%) patients. Surgical site infection was detected in 19 (28%) patients and anastomotic leak was detected in 4 (6%) patients. Mortality was observed in the first 7 days in 1 (1.5%) patient with leakage. The patient who developed mortality was Charlson Comorbidity Index (CCI) 6 and cause of death was pulmonary embolism. In 6 (9%) patients, ileus developed in the early postoperative period (first 7 days). 7 (10%) patients needed postoperative intensive care. The mean postoperative hospital stay was ± SD = 15,11 ± 9,12 days.

Conclusion: The morbidity and mortality after stoma closure is not negligible. After the Hartmann procedure, we think that optimal closure interval, appropriate patient selection, patient's comorbidity load, intensive care unit at the center, and closure at specialized or experienced centers will be appropriate.

Keywords: Hartmann procedure; complication; hartmann colostomy closure

Giriş

Ostomi için ileumun bir segmentinin yanısıra tüm kolonik segmentler diversiyon amaçlı kullanılabilir. Hartmann prosedürü(HP), kolonik neoplastik obstrüksiyonlu hastalarda anastomoz kaçağına bağlı mortaliteyi azaltmak için tanımlanan ilk diversiyon yöntemidir.[1] Genellikle primer anastomozun mümkün olmadığı komplike divertikülit, ateşli silah yaralanmaları ve volvulus gibi acil durumlarda, özellikle sepsis ve multiorgan fonksiyon bozukluğu nedeniyle hemodinamik instabilite olan hastalarda uygulanmıştır.[2]

Stoma prosedürleri genellikle geçici olacağı düşüncesiyle gerçekleştirilmektedir ancak vakaların %74'e kadarında kalıcı olabilir. Bu durum, yaş ve hastanın sahip olduğu çeşitli komorbiditelerden kaynaklanmaktadır.[3] İntestinal pasajı tekrar sağlamak bazen zor olabilir ve kapatılma zamanlamasına etki eden birçok faktör de bulunabilir. Hekim bu prosedürü karmaşık bir cerrahi olarak görmelidir.[4]

Bunlara ilaveten, hastaların komorbiditeleri nedeniyle komplikasyon oluşturma riskleri yüksektir. Bu nedenle dikkatli hasta seçimi esastır. Literatürde %55'e kadar komplikasyon oranı ve %4'e kadar mortalite tarif edilmiştir. Komplikasyonları tahmin etmek ve tanımlamak son derece önemlidir.[5] Bu çalışmanın amacı, HP yapılan hastaların intestinal devamlılığın restorasyonundan sonra klinik seyirlerindeki olumsuz etmenleri değerlendirmekti.

Gereç ve Yöntemler

Hastaların Analizi

1 Ocak 2012-31 Aralık 2017 tarihleri arasında kliniğimizde Hartmann kolostomi kapatılan 66 hastanın demografik verileri, kolostomi açılma nedenleri, postoperatif yatış süreleri, yoğun bakım ihtiyacı, mortalite/morbidite varlığı, Amerikan Anesteziyoloji Derneği Skoru (ASA) ve komplikasyonları tanı/tedavi yaklaşımları ile ilgili veriler retrospektif olarak elektronik ortamdaki kayıtlarından elde edildi. Çalışma Helsinki İlkeler Deklarasyonu'na uyularak gerçekleştirildi. Çalışmaya dahil edilen tüm insanlar bilgilendirilmiş onam formunu imzalamıştır. Lokal etik kurul onayı mevcuttur.

Mortalite, Hartmann kolostomi kapatıldıktan sonraki ilk 30 gün içerisinde gerçekleşen ölümleri kapsamaktadır. Morbidite, hastanede kalışta artışa veya tıbbi müdahaleye ihtiyaç duyulmasına neden olan herhangi bir komplikasyon türü olarak tanımlandı.

Postoperatif ileus, anastomoz kaçağı, yara yeri enfeksiyonu, intestinal obstrüksiyon, pulmoner emboli ve eviserasyon komplikasyon olarak tanımlandı. Anastomoz kaçağı, peritonite yol açan anastomotik ayrışma, pelvik drenajda fekal içeriğin varlığı ve bilgisayarlı tomografi'de görülen oral veya rektal kontrast sızıntısı ile anastomozu çevreleyen bir abse varlığı olarak tanımlandı. Kaçak olan tüm hastalara yeni girişim yapılmadı. Sadece jeneralize peritonit, sepsis veya multiorgan disfonksiyonu olanlar tekrar ameliyat edildi. Yara yeri enfeksiyonu, cilt eritemi, lokal ısıda artış ve antibiyotik veya lokal müdahale gerektiren olgular olarak tanımlandı.

Charlson comorbidity index(CCI), hastanın komorbiditelerini sınıflandırmanın bir yöntemidir. Her bir komorbidite, mortalite riskine bağlı olarak 1-6 arasında bir skora sahiptir. Skorlar, tek bir komorbidite skoru vermek için toplanır.

İstatiksel Analiz

İstatistiksel analizler, Statistical Package for the Social Sciences(SPSS) for Windows (13.0 version) programında yapıldı. Veriler ortanca (min-max) olarak ifade edildi. Sayısal veriler yüzde (%) ile ifade edildi.

Bulgular

66 hastanın 46(%69)'sı erkek ve 20(%31)'si kadındı. Bunların medyan yaşları 54(18-85) idi. Çalışmaya dahil olan hastaların 21(%32)'i kolorektal kanser, 11(%17)'i sigmoid volvulus, 4(%6)'ü divertikülit perforasyonu ve geri kalan 30(%45) hasta diğer nedenlerle (12 hasta sigmoid volvulus, 2 hasta yüksek enerjili patlama ve 2 hasta iskemik kolit v.b.) Hartmann kolostomi açılmış hastalardı. Ostomilerin ortalama kapatma süreleri 4±3 aydı. ASA skoru 19(%28) hastada II ve 47(%72) hastada III'dü.

Postoperatif dönemde 19(%28) hastada cerrahi alan enfeksiyonu ve 4(%6) hastada anastomoz kaçağı tespit edildi. Anastomoz kaçağı tanısı klinik, laboratuvar ve görüntüleme (Abdominal Tomografi) bulguları ile konuldu. Bunların 1(%1,5)'inde postoparatif ilk 7 günde mortalite gelişti. Mortalite gelişen hastanın Charlson Comorbidity Index (CCI)'i 6 ve ölüm nedeni de pulmoner emboliydi. 2 hastada yeniden Hartmann kolostomi yapıldı. Geri kalan 1 hasta da medikal tedavi ile tam iyileşme sağlandı. 6(%9) hastada postoperatif erken dönemde (ilk 7 gün) ileus gelişti. Medikal tedavi ve takiplerinde hastaların tamamında pasaj sağlandı. 7(%10) hastada postoperatif yoğun bakım ihtiyacı oldu. Yoğun bakım ihtiyacı olan 7 hastanın 5'inde yara yeri enfeksiyonu 2'sinde postoperatif ileus gelişdi. Hastaların postoperatif yatış süreleri ortalama±SD=15,11±9,12 gündü (Tablo-1).

Tablo-1: Hartmann kolostomi kapatılan hastaların demografik özellikleri, cerrahi endikasyonlar, komplikasyonlar, ASA skoru ve postoperatif diğer problemler

Hasta Özellikleri		n (%)
Cinsiyet	Erkek	46 (69)
	Kadın	20 (31)
Yaş ortanca (Min-Max)		54 (18-85)
Hartmann Kolostomi Endikasyonları	Kolorektal Kanser	21 (%32)
	Sigmoid Volvulus	11 (%17)
	Divertikülit Perforasyonu	4 (%6)
	Diğer Nedenler	30 (%45)
Komplikasyon	Cerrahi Alan Enfeksiyonu	19 (%28)
	Anastomoz Kaçağı	4 (%6)
Anastomoz Kaçağı Yönetimi	Medikal Tedavi	2 (%3)
	Tekrar Hartmann Kolostomi	2 (%3)
Mortalite		1 (%1,5)
Postoperatif İleus	Var	6 (%9)
	Yok	60 (%91)
Yoğun Bakım İhtiyacı	Var	7 (%10)
	Yok	59 (%90)
ASA skoru	II	19 (%28)
	III	47 (%72)
Hartmann Kolostomi Kapatma Süresi Ortalama±SD		4±3 ay
Postoperatif Yatış Süresi Ortalama±SD		15,11±9,12 gün
Charlson Comorbidity Index (CCI)	≥6	20 (%30)
	<6	46 (%70)
Toplam		66 (%100)

Tartışma

Cerrahi tekniklerdeki ilerlemelere ve deneyimlere rağmen, HP sonrası bağırsak devamlılığının restorasyonu hala yüksek morbidite ve mortalite riski ile ilişkilidir. HP, literatürde sırasıyla % 50 ve 10'a varan morbidite ve mortalite oranları bildirilen önemli bir cerrahi işlemdir.[6] Çalışmamızda mortalite 1(%1,5) hastada pulmoner emboliye bağlı olarak gelişti. Bu oranın literatüre göre oldukça düşük olduğu söylenebilir. Literatürde, hastaların yaklaşık yarısının, Hartmann'ın kapatılma riskine dayanarak ameliyatı reddettiği bildirilmiştir.[7] Bu hastaların, kalıcı bir stoma ile önemli yaşam kalitesi sorunları ile karşı karşıya kaldığı ileri sürülmüştür.[8]

Yapılan bir derlemeye göre, Hartmann kolostomi kapatılan(HKK) hastaların % 67'sinin ASA skoru I veya II olarak sınıflandırılmıştır.[6] Oysa bu çalışmada HKK hastaların %72'si ASA III ve %28'i ASA II olarak tanımlandı. Farklı olarak çalışmamızdaki ASA riski derlemeye göre oldukça yüksek bulunmuştur.

Horesh ve ark.[9]'nın yapmış olduğu çalışmada HP yapılmasının en önemli nedenleri % 36,1 ile divertikülit perforasyonu ve % 31,8 ile obstrüktif kolonik kanserler olarak tanımlanmıştır. Aynı çalışmada HKK'nın yaşam kalitesini iyileştirmeyi amaçlayan, ancak önemli bir komplikasyon riski ile ilişkili olan büyük bir operasyon olduğu göz önüne alındığında, cerrahların bu prosedürü yüksek performansa sahip, zinde ve uyumlu olan hastalara önerme konusunda daha istekli olduğu görülmektedir. Çalışmamızda ise; sırasıyla kolorektal kanserler, sigmoid volvulus ve divertikülit perforasyonunun HP endikasyonları arasında olduğu görülmüştür.

Roig ve ark.[10]'nın yaptığı çalışmada, HKK hastaların oranlarında erkek cinsiyet lehine anlamlı bir fark olduğu gösterilmiştir. Buna paralel olarak bu çalışmada HKK hastaların oranı erkek hastalarda daha yüksek olduğu görülmektedir.

Birçok çalışmada, HKK hastaların komplikasyon oranı yaklaşık % 25-45 arasında değişim gösterdiği bildirilmiştir.[11] Literatürde, HKK hastaların en sık karşılaşılan komplikasyonu yara yeri enfeksiyonu olarak bildirilmiştir(9, 10). İspanya'da yapılan çok merkezli bir çalışmada, HKK hastaların % 25'inden fazlasında cerrahi alan enfeksiyonu geliştiğini bildirmişlerdir.[12] Anastomoz kaçak oranları, birçok kolorektal prosedür için yapılanlara benzer, oldukça büyük birkaç yeni çalışmada yaklaşık % 4 oranında görülmüştür.[13,14] Bu çalışmada da HKK hastalarda en sık cerrahi alan enfeksiyonu görülmüştür. Bunlara ilaveten sırasıyla, postoperatif ileus ve anastomoz kaçağı komplikasyon olarak görüldü. Genel olarak komplikasyon oranımız (%45) literatürle uyumlu bulundu.

Hartmann kolostomiyi kapatmanın zamanlaması halen tartışmalı bir konudur. Optimal zamanın hastanın karnındaki inflamatuar durumun tamamen çözülme sürecidir. Bu süreç çoğu zaman 6 ay kadar sürebilmektedir. Revers süresinin daha kısa olması rektal güdük atrofisini önleyebildiği ileri sürülmüştür(15). Bu çalışmada HP uygulama ve HKK intervali ortalama 4 ay olarak bulunmuştur.

Fonseca ve ark.[15] yoğun bakım ihtiyacı olan hastalarda komplikasyon gelişme ihtimalinin arttığını, hastanede kalış sürelerinin uzadığı ve bunların ek komorbiditelerinin daha fazla olduğunu ileri sürmüştür. Çalışmamızda da yoğun bakım gereken hastalarda cerrahi alan enfeksiyonu ve anastomoz kaçağı oranı daha yüksek bulunmuştur. İlaveten bu çalışmada 20(%30) hastanın CCI'i ≥6 tespit edilmiştir.

HKK' da yaşanan sorunlar dikkate alındığında, son dönemde yayınlanan bir meta-analizde loop kolostomi ile karşılaştırıldığında loop ileostomi kapatılmasında, daha az yara yeri enfeksiyonu, daha az insizyonel herni oluşturduğu ve genel komplikasyonlar açısından bir fark olmadığı ileri sürülmüştür.[16] Gerekli olan hastalarda HP elbet uygulanabilir, fakat böyle bir durumda mümkünse rezeksiyon anastomoz ve loop ileostominin olası avantajları açısından tercih edilmesi daha uygun olabilir.

Sonuç

Stoma kapanmasından sonraki morbidite ve mortalite önemsiz bir durum değildir. HP'nden sonra optimal kapatma intervali, uygun hasta seçimi, hastanın komorbidite yükü, merkezde yoğun bakım varlığı ve özelleşmiş veya deneyimli merkezlerde kapatılma işleminin yapılmasının uygun olacağını düşünmekteyiz.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Turkish Journal of Clinics and Laboratory

To cite this article: Akkaş EA, Güvenç O. Boyun ve mediasten tutulumlu hodgkin lenfoma olgularında Butterfly VMAT tekniği avantajlı mıdır?. Turk J Clin Lab 2020; 4: 274-281.

Orjinal Makale

Boyun ve mediasten tutulumlu hodgkin lenfoma olgularında Butterfly VMAT tekniği avantajlı mıdır?

Is Butterfly VMAT technique advantageous in hodgkin lymphoma patients with neck and mediastinal involvement?

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Öz

Amaç: Bu çalışmada, erken evre Hodgkin lenfoma (HL) tanılı bilateral boyun ve mediasten yerleşimli genç kadın ve erkek olgularda, üç boyutlu konformal radyoterapi (3DCRT) ile volumetric modulated arc therapy (VMAT) ve butterfly VMAT tekniklerinin dozimetrik olarak karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Erken evre HL'lı 20 hastaya radyoterapi uygulandı. Tüm plan verileri, hedef hacim ve kritik organ doz hacim histogramları karşılaştırıldı. Her üç teknik için konformite indeksi, homojenite indeksi ve % V107 farklılıkları değerlendirildi.

Bulgular: Sağ meme maksimum, V25, V30 ve sol meme maksimum, V20, 25, 30 değerleri ise 3DCRT planlamada diğer VMAT planlarında elde edilen değerlerden daha yüksek idi. Bu da istatistiksel olarak anlamlı bulundu. Akciğer V5 değerleri 3DCRT planlamasında, VMAT planlarından daha düşüktü ve V20, 25,30 değerleri ise VMAT planlarından istatistiksel olarak daha yüksekti. Sağ ve sol parotis ortalamaları, V5,20 25, 30 değerleri butterfly VMAT planlamasında diğer planlara göre anlamlı olarak daha düşüktü. Sağ parotis V20, V25 değerinin butterfly VMAT planlamasında, ikili karşılaştırmalarda VMAT planından daha düşük olduğu bulunmuştur.

Sonuçlar: Memede 20 Gy ve üzerinde VMAT, butterfly VMAT, 20 Gy ve altında ise 3DCRT tekniğinin daha avantajlı olduğu görülmektedir. Parotis dozları açısından ise butterfly VMAT'ın daha avantajlı olduğu görülmektedir.

Anahtar kelimeler: Hodgkin lenfoma; radyoterapi; butterfly

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Doi: 10.18663/tjcl.776107

Abstract

Aim: In this paper, comparative planning for Three dimensional conformal (3DCRT), volumetric modulated arc therapy (VMAT) ve butterfly VMAT in a young female and male cohort with bilateral neck and mediastinal involvement diagnosed with early-stage Hodgkin's lymphoma (HL) and we report whether the butterfly technique is advantageous.

Material and Methods: 20 patients with early-stage HL were treated radiotherapy. All plan solutions were compared by target volume and critical organ dose-volume histograms. The conformity index, homogeneity index, and V107% differences were evaluated for all three techniques.

Results: Right breast max, V25, V30 and left breast max V20,25,30 values in 3DCRT planning. It was found to be higher than the values obtained in the plans, which was found to be statistically significant. Lung V5 values were lower in 3DCRT planning than VMAT plans, and V20, 25,30 values were statistically higher than VMAT plans. Right, and left parotid means, V5,20 25, 30 values were significantly lower in butterfly VMAT planning compared to other plans. The right parotid V20, V25 value was found to be lower in butterfly-VMAT planning than in the VMAT plan in bilateral comparisons.

Conclusion: VMAT, butterfly VMAT over 20 Gy in the breast, and 3DCRT techniques under 20 Gy are more advantageous in the examination of dose volumes of the organs at risk. İn terms of parotid doses, butterfly VMAT seems to be more advantageous.

Keywords: Hodgkin's lymphoma; radiotherapy; butterfly

Giriş

Radyoterapi (RT), erken evre Hodgkin lenfomalı (HL) hastalarda kemoterapiyi de içeren kombine tedavi modalitesinin önemli bir bileşenidir. Kombine tedavi modalitesi ile %85–93 oranında kür sağlanır [1 , 2]. HL'ların genç yaş grubunda sık gözlenmesi ve yüksek kür oranları nedeniyle tedaviye bağlı akut ve geç komplikasyonların en aza indirilmesi en önemli hedeftir [1 , 3]. Özellikle ekstended-field ve yüksek doz RT ile tedavi edilen olgularda, kardiyak hastalıklar ve sekonder malignensiler en önemli geç yan etkilerdir. Bu amaçla klinisyenler yüksek kür oranları sağlarken, yan etkileri azaltmak için RT alan ve dozunda modifikasyonlara gitmiştir [4].

HL'larda, modern RT yaklaşımları ile daha düşük dozlarda (20–30 Gy), daha küçük hacimlerin ışınlanması, risk altındaki organ (OAR) dozlarının azalmasına neden olur. Böylece daha düşük oranda RT'ye bağlı geç toksisite gözlenir. RT teknolojisindeki gelişmelere paralel olarak hedef hacim dozlarından taviz vermeden, OAR'lar için en iyi doz dağılımını sağlayan tekniklerin belirlenmesi için çalışmalar devam etmektedir [5]. Geçmişte 2- boyutlu tedavi uygulanırken, günümüzde üç boyutlu konformal radyoterapi (3DCRT), intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) uygulamaları artmıştır. Lenfomalarda sıklıkla geniş alanlardan ışınlama yapıldığı için sıklıkla 3DCRT yeterlidir. Özellikle boyun ve mediasten yerleşimli HL'larda ise OAR dozlarını azaltmak için IMRT ve VMAT daha avantajlı olabilir. Literatürde, farklı IMRT tekniklerini içeren çalışmalarda mediastinal HL'lı kadın hastalarda "butterfly" (BF) tekniğinin dozimetrik olarak avantajlı olduğu gösterilmiştir. Özellikle, BF VMAT'ın, hedef hacimlerde yüksek konformalite ve OAR'larda maksimum koruma sağladığı gösterilmiştir [5].

HL hasta popülasyonu için, doz volüm histogramı (DVH) önerileri ve Normal Doku Komplikasyon Olasılığı (NTCP) modelleri geliştirilmiştir. Bu modeller ile akciğer toksisitesi, kardiyovasküler hastalıklar ve hipotiroidizm gibi akut ve geç yan etkileri azaltmayı amaçlayan planlama optimizasyon prosedürleri oluşturulmuştur [5].

Bu çalışmada, Involved-site Radiotherapy (ISRT) planlanan erken evre HL tanılı bilateral boyun ve mediasten yerleşimli olgularda, 3DCRT ile farklı IMRT tekniklerinin (butterly VMAT ve VMAT) dozimetrik olarak karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler

Hasta ve tedavi özellikleri

Çalışma onayı, Sağlık bilimleri Üniversitesi Ankara Dr. Abdurrahman Yurtaslan Onkoloji Sağlık Uygulama ve Araştırma Merkezi Tıpta Uzmanlık ve Eğitim Kurulu (TUEK) tarafından Helsinki Deklarasyonuna göre 05.12.2017/24 numaralı karar ile onaylanmıştır. Çalışmaya dahil edilen hastalardan bilgilendirilmiş onay formu alınmıştır.

Çalışmamıza, Nisan 2014-Haziran 2018 tarihleri arasında kli-

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niğimize başvuran, bilateral boyun ve mediastinal tutulumu olan erken evre (I-II) HL tanılı 10 kadın ve 10 erkek, toplam 20 hasta dahil edildi. Ortanca yaş 25 (aralık, 18-32) idi. Tüm olgularda başvuru sırasında mediastinal, bilateral hiler, supraklaviküler ve üst boyun tutulumu vardı. Hiçbir hastada ekstranodal tutulum yoktu. Aksiller tutulumu olan hastalar çalışma dışı bırakıldı. Tüm hastalar kemoterapi öncesi kontrastlı Bilgisayarlı Tomografi (CT) ve pozitron emisyon tomografisi (PET)/CT ile evrelendi. Evreleme sonrası olgular The European Organisation for Research and Treatment of Cancer Lymphoma Group (EORTC) risk gruplamasına göre favorabl veya unfavourable olarak sınıflandırıldı. Takiben olgulara 3 ya da 4 kür ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) kemoterapisi uygulandı. Kemoterapi sonrası yanıt değerlendirmesi amacıyla çekilen CT ve PET/CT'de tüm olgularda tam yanıt gözlendi. CMT'nin bir parçası olarak tüm olgulara RT planlandı.

Radyoterapi Simülasyonu

Olgulara son kemoterapiden 3-4 hafta sonra, 4-dimensional CT (4DCT) ile kontrastsız, 3 mm kesit kalınlığında, akciğer boardu (ofix® curve board) ve baş-boyun maskesinden (Radon® Thermoplastic IMRT-A Head Shoulder Mask) oluşan immobilizasyon cihazları kullanılarak, kollar akimbo pozisyonunda olacak şekilde planlama amaçlı CT'si çekildi.

Radyoterapi Planlama

Tüm olgulara, International Lymphoma Radiation Oncology Group (ILROG) Guideline'ına göre ISRT planlandı [6]. Tüm hastalarda clinical target volüme (CTV) ve OAR'lar, aynı radyasyon onkoloğu tarafından çizildi Kemoterapi öncesi PET/CT görüntüleri ile 4DCT görüntüleri, Eclipses Image Registration modüle kullanılarak füzyon yapıldı. CTV, ILROG guideline'ına göre, ISRT prensibince çizildi. Planing target volume (PTV), CTV'ye 10 mm izotropik marjin verilerek oluşturuldu. OAR olarak; kalp, akciğerler, sağ ve sol parotis, tiroid, spinal kord, left anterior descending artery (LAD) ve kadınlarda sağ ve sol meme konturlandı.

RT planlaması için VarianTrilogy (Varian Medical Systems, Palo Alto, CA) cihazı tedavi planlama sistemi (Eclipse versiyon 11.0.31) kullanılarak üç farklı teknikte 3DCRT, SingleArc ve Butterfly-Arc tedavi planları yapıldı. RT dozu 15 fraksiyonda, 30 Gy olarak reçete edildi.

3DCRT, wedge tekniğiyle 6–18 MV foton enerji kombinasyonu kullanılarak planlandı. Boyun kısmı için sağ-sol (90 ve 270 derece) wedge'li alan açılırken, mediasten alanı için ön-arka yarı kesicili alan kullanıldı. Hesaplamalar The Analytical Anisotropic Algorithm (AAA) ile yapıldı.

SingleArc ve Butterfly-Arc (MultipleArc) tekniğinde 6 MV enerji kullanıldı. Single- Arc planlar kol açıları yasaklanarak (240-300 ve 60-120 derece yasaklanacak şekilde), 1 isocenter-2 full ark olarak tam tur dizayn edildi. Multiple arc için tam tur, kol açısı yasaklanarak yapılan arc planına ek olarak 90 derece masa rotasyonu ile AP-PA 35–335 derecede 1 isocenter-2 yarım rotasyon arc planı eklendi.

Hedeflenen PTV kapsanması ve OAR dozlarını elde etmek için, Arc planları yapıldıktan sonra, hedef kapsanmasını korurken OAR dozlarının ilk planlamalarda elde edilen doz değerlerinin altına düşürmek hedeflendi. Her hasta için optimal bir plan elde edilinceye kadar çoklu planlamalar yapıldı. Hedef hacim ve OAR'lar için tedavi planlama hedefleri Tablo 1'de verilmiştir [7].

Tablo 1. Tedavi planında hedeflenen OAR dozları

OAR	Parametre	Hedef
PTV	D ortalama(Gy)	30
	V % 90 (%)	99
	V% 95 (%)	95
	V % 107 (%)	1
Meme	V 4Gy (%)	50
	V 10Gy (%)	33
Akciğer-PTV	V 5Gy (%)	50
	V 10Gy (%)	33
Tiroid	V 18Gy (%)	50
	V 25Gy (%)	33
Parotis	ortalama (Gy)in tek gland	≤ 26
Kalp	ortalama (Gy)	<15
	V 7.7Gy (%)	50
	V 15Gy (%)	33
LAD	ortalama (Gy)	<15
Spinal kord	Dmax	30

OAR: Risk altındaki organlar, PTV:Planlanan hedef volüm, LAD:Left anterior descending artery

Kümülatif DVH'ler ile kantitatif değerlendirme yapıldı. PTV için analiz edilen parametreler; Dmin, Dmax, Dortalama, V90, V95, V107, konformite indeksi (CI) ve homojenite indeksi (HI) olarak belirlendi. Planların uygunluğu, Van't Riet ve ark.'larının önerdiği CI kullanılarak değerlendirildi [8]. ICRU 62'ye göre CI = Tedavi edilen hacim/PTV hacmi formülü kullanılarak hesaplandı [9]. PTV'de tedavi edilen hacmin tamamen kapsanıp kapsanmadığını ifade eder. CI=1 ideal konformasyon, CI> 1 ışınlanan hacim sağlıklı dokuyu kapsar, CI <1 hedef hacim yalnız kısmen ışınlanır, olarak yorumlanır. HI için ise HI = (D2 -D98) /Dp x100 % formülü kullanılmıştır. Bu formülde D2 ve D98, seçilmiş hacmin %2'si ve %98'inin aldığı dozlardır. Dp ise tanımlanan dozdur.

PTV sarımını doğrulamak için, RT tedavisinden önce, günlük ortogonal kilovoltage (Kv) ve haftalık cone-beam CT (CBCT) ile görüntüleme yapıldı. Günlük görüntülemelerinde, PTV'nin %100 ve %95 izodoz hatları ve dolayısıyla CTV sarımı da doğrulandı.

Uygun kaydırmalar yapıldı. Her hasta, kendisi için yapılan her üç plandan dozimetrik olarak en avantajlı plandan tedaviye alındı.

İstatistik Analiz

Tüm veriler, SPSS version 22 (IBM Corp., Armonk, New York, USA) istatistik programı kullanılarak analiz edildi. İki tedavi planını karşılaştırmak için Wilcoxon matched-paired ve signed-rank testi, üç tedavi planı arasındaki sonuçları karşılaştırmak için ise Friedman testi kullanıldı. İstatistiksel önemi belirlemek için p değeri <0.05 anlamlı olarak kabul edildi.

Bulgular

Hedef hacimler

Hedef hacimler için üç planlama tekniğinin dozimetrik karşılaştırılması Tablo 2'de verilmiştir.

Tablo 2. Hedef hacimler için üç planlama tekniğinin dozimetrik karşılaştırılması

PTV	3DCRT	VMAT	Butterfly- VMAT	P değeri
Dortalama(Gy)	30,8	30,2	30,2	0,13
V90%(%)	99	99,4	99,4	0,08
V95%(%)	95,1	96,5	96,5	0,74
V107%(%)	21,4	0,14	0,19	0,001
Dmin (Gy)	21,5	22,1	21,9	0,60
Dmax (Gy)	33,7	32,7	32,7	0,008
CI	0,98	0,96	0,96	0,13
HI	1,45	1,16	1,14	0,01

PTV:Planlanan hedef volüm, 3DCRT: Üç-boyutlu konformal radyoterapi, VMAT:Volumetrik modüle ark terapi, Butterfly-VMAT:Butterfly- Volumetrik modüle ark terapi, CI:Konformite indeksi, HI: Homojenite indeksi

Üç planlama tekniği karşılaştırıldığında PTV kapsanması (Dmean, V%90, V%95, Dmin,) açısından anlamlı fark gözlenmemiştir (Tablo 2). CI açısından bakıldığında tedavi planları arasında fark gözlenmemesine karşın (3DCRT planlamada, ideal değer olan 1 'e en yakın değer elde edilmiştir, CI: 0,98 idi), HI'nin VMAT planlarında, 3DCRT planı ile karşılaştırıldığında üstün olduğu görülmüştür (1,16 ve 1,14 vs. 1,45, p=0,01). V107(%) ve Dmax değerleri, 3DCRT planlama tekniğinde en yüksek değerlere sahipti.

Kritik organ dozları

Üç tedavi planlama tekniği karşılaştırıldığında, bilateral akciğer için ortalama dozlarda fark gözlenmezken, düşük doz alan hacim (V5) 3DCRT planlamada, yüksek doz alan hacimler (V20, V25, V30) ise VMAT planlarında istatistiksel anlamlı olarak yüksek bulunmuştur (p <0,05).

Akciğer V5 değerleri; ikili karşılaştırmalarda butterfly VMAT planlamada, VMAT planlamaya göre istatistiksel olarak anlamlı düşük bulundu (p: 0,012).

Sağ meme mean, V5, V20 ve sol meme mean ve V5 değerleri 3DCRT planlama için daha düşük değerlerle daha avantajlı ve istatistiksel olarak anlamlı bulundu ancak sağ meme maks, V25, V30 ve sol meme maks V20,25,30 değerleri ise 3DCRT planlamada diğer VMAT planlarında elde edilen değerlerden daha yüksek idi. Bu da istatistiksel olarak anlamlı bulundu (p <0,05).

LAD (Left anterior descending artery) V5, 20, 25,30 değerleri, 3DCRT planlamada VMAT planlarına göre istatistiksel olarak anlamlı yüksek bulundu (p <0,05).

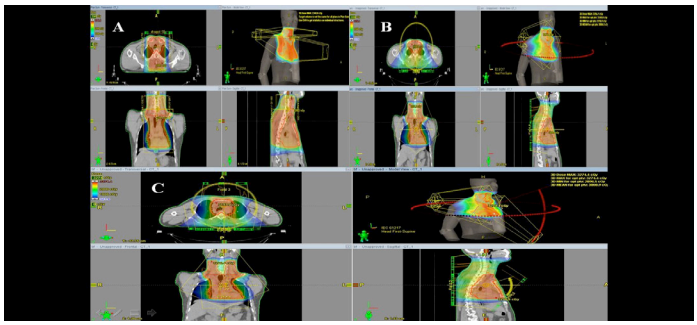
Kalp mean, V4, 5, 10, 20, 25 değerleri 3DCRT planlamada, VMAT planlarına göre istatistiksel olarak anlamlı yüksek bulundu (p <0,05).

Spinal kord mean, V5,20 25, 30 değerleri de; 3DCRT planlamada, VMAT planlarına göre istatistiksel olarak anlamlı yüksek bulundu (p <0,05).

Troid mean, V18, 25 dozları; VMAT planlamada, 3DCRT ve Butterfyl-VMAT planlamaya göre daha düşüktü ve istatistiksel olarak anlamlıydı (p:0,001, p:0,085, p:0,001).

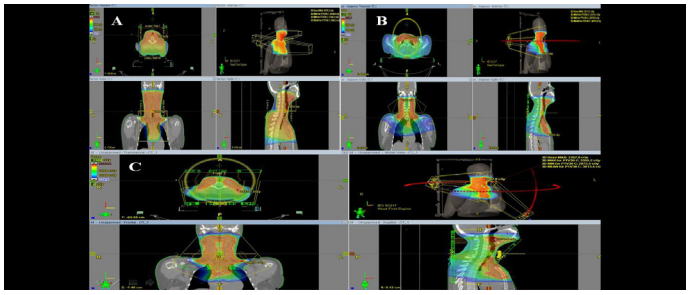
Sağ ve sol parotis mean, V5,20 25, 30 değerleri; Butterfyl-VMAT planlamada diğer planlara göre istatistiksel olarak anlamlı düşük dozlar bulundu. Sağ parotis V20 değeri ikili karşılaştımalarda butterfl-VMAT planlamada, VMAT plana göre daha düşük bulundu ve istatistiksel olarak anlamlı kabul edildi (p:0,033). Sağ parotis V25 ise; butterfl-VMAT planlamada, VMAT plana göre daha düşük bulundu ancak istatistiksel olarak anlamlı kabul edilmedi (p:0,06).

Kritik organ dozları için üç planlama tekniğinin dozimetrik karşılaştırılması Tablo 3'te verilmiştir. Resim 1 (A, B, C) 'de erkek hastalar için resim 2 (A, B, C)' de kadın hastalar için üç ayrı tedavi planına ait doz dağılımı gösterilmektedir.



Resim 1. Erkek hastalar için üç ayrı tedavi planına ait doz dağılımı

(A:3DCRT, B: VMAT, C: Butterfly-VMAT)



Resim 2. Kadın hastalar için üç ayrı tedavi planına ait doz dağılımı

(A: 3DCRT, B: VMAT, C: Butterfly-VMAT)

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Tablo 3. Kritik organ dozları için üç planlama tekniğinin dozimetrik karşılaştırılması

Risk altındaki organ		3DCRT	VMAT	Butterfly-VMAT	P değeri
Sağ meme	V 30	% 1	% 0	%0	0,05
	V 25	% 1,7	% 0,1	%0,1	0,02
	V 20	% 2	% 0,4	% 0,7	0,01
	V 5	% 4,8	% 11,2	% 10,7	0,02
	Ortalama Doz, Gy	1,3	1,8	1,9	0,005
	Max Doz, Gy	21,8	13,6	14,7	0,27
Sol meme	V 30	% 0,3	% 0	% 0	0,05
	V 25	% 0,9	% 0	% 0	0,01
	V 20	% 1,2	% 0,03	% 0,2	0,02
	V 5	% 3,7	% 9,5	%8,1	0,01
	Ortalama Doz, Gy	1	1,5	1,5	0,005
	Max Doz, Gy	20,2	14	14,9	0,276
LAD	V 30	% 16,9	% 5,5	% 7	0,22
	V 25	% 32,5	% 22,2	% 22,3	0,005
	V 20	% 34	% 23,6	% 23,9	0,001
	V 5	% 46,8	% 40,1	% 40,3	0,01
	Ortalama Doz, Gy	11	9,3	9.6	0,07
Kalp	V 30	% 7,5	% 7	% 7,6	0,51
	V 25	% 25,1	% 13,7	% 13,9	0,001
	V 20	% 28	% 17,2	% 17,2	0,001
	V15	%31,6	% 20,1	%20,4	0,001
	V10	%37,4	% 24,5	%25	0,001
	V 5	% 42	% 31,7	% 32,8	0,001
	V4	% 43,7	% 35,1	%35,9	0,001
	Ortalama Doz, Gy	10,4	7.5	7,6	0,005
Total Akciğer	V 30	% 9,1	% 1,7	% 1,7	0,001
	V 25	% 18,7	% 9,9	% 10,1	0,001
	V 20	% 21,4	% 18,4	%16,8	0,001
	V 5	% 36,3	% 49,5	% 48,8	0,001
	Ortalama Doz, Gy	8,3	8,8	8,9	0,6
Spinal kord	V 30	% 33,5	% 0,2	% 0	0,001
	V 25	% 54,6	% 17,2	% 15	0,001
	V 20	% 55,5	% 32,7	% 33,2	0,001
	V 5	%61,9	% 57	% 57,4	0,001
	Ortalama Doz, Gy	17,6	12	12,2	0,001
Sağ parotis	V 30	% 30,6	% 12,4	%10,5	0,02
	V 25	% 71,2	% 40,6	%33,3	0,001
	V 20	% 76,2	% 54,3	% 42,5	0,001
	V 5	% 86,9	% 77,6	% 66,3	0,001
	Ortalama Doz, Gy	23,8	17,9	16,1	0,001
Sol parotis	V 30	% 37,4	% 54,4	% 13,4	0,05
	V 25	% 74,6	% 45,6	% 40,4	0,001
	V 20	% 78,2	% 57,4	% 52,1	0,001
	V 5	% 86,8	% 78,5	% 77,4	0,02
	Ortalama Doz, Gy	23,7	19,4	18,5	0,001
Tiroid	V 18	%100	%96	%96	0,08
	V 25	%99,8	%79,2	%81,6	0,001
		31,6	27,3	27,6	0,001

3DCRT: Üç-boyutlu konformal radyoterapi, VMAT: Volumetrik modüle ark terapi, Butterfly-VMAT:Butterfly- Volumetrik modüle ark terapi, LAD: Left anterior descending artery

Tartışma

IMRT'nin, kritik organlarda doz düşüklüğüne yol açıp açmayacağı ve geç komplikasyon oranlarını artırıp artırmayacağı merak konusu olmuştur. Farklı IMRT yaklaşımlarının önemli klinik sonuçları ve kritik organları korumayı artırabileceğine dair artan kanıtlar vardır. Birçok çalışma, lenfoma hastaları için konvansiyonel 2D, 3DCRT ve IMRT planlarından elde edilen tedavi sonuçları olan OAR dozlarını, karşılaştırmıştır.

Goodman ve ark. ları bulky mediastinal HL veya nonhodgking lenfoma tanılı mediastinal radyoterapi alan 16 hastayı analiz etmiştir [10]. Bu çalışmada, PTV dozu, konvansiyonel anterior-posterior / posterior-anterior plana kıyasla IMRT ve 3DCRT planlama yöntemlerinde daha iyi olarak bulunmuştur.

Fiandra ve ark.nın , erken evre mediastinal tutulumu olan on HL tanılı kadın hastada 3DCRT ve IMRT planlarını karşılaştırdığı çalışmada , PTV sarımını (V% 95 (%) > 95) birbirine benzer

değerlerde bulmuşlardır [11]. Bizde çalışmamızda, PTV sarımını benzer değerlerde bulduk.

Jackson ve ark. ları ise hem ortalama akciğer dozunu, hem de pnömoni olasılığını, 2D ve 3D planlara kıyasla, IMRT planlarında daha düşük olarak bulmuşlardır [12]. Bununla birlikte, Goodman ve ark. ise en az 20 Gy alan akciğer hacminin (V20), IMRT planı ile arttığını bulmuşlardır [10]. Çalışmamızda ise Akciğer V5 değerleri 3DCRT planlamada, IMRT planlarına göre daha düşük, V20, 25, 30 değerleri ise istatistiksel olarak IMRT planlarına göre daha yüksek bulunmuştur. Akciğer V5 değerleri, VMAT planlarının ikili karşılaştımalarında ise butterfly-VMAT planlamada, VMAT planlamaya göre istatistiksel olarak anlamlı düşük bulunmuştur (p: 0,012). Fiandra ve ark. da karşılaştırdığı tüm IMRT tekniklerinde, akciğer V20 değerlerini, 3DCRT'ye göre düşük ancak V5 değerlerini ise yüksek bulmuşlardır [11].

Girinsky ve ark.ise mediastinal HL hastalarında, IMRT, 3DCRT ve anterior-posterior / posterior-anterior planlarını karşılaştırmışlardır. IMRT planlamada, kalp, koroner arterler, özefagus ve spinal kord gibi kritik organ doz dağılımını daha iyi bulmuşlardır. Bununla birlikte, konvansiyonel tedavide; 3DCRT ve IMRT'den biraz daha düşük bir akciğer ortalama dozu bulmuşlardır. IMRT'ye benzer fakat 3DCRT'den anlamlı bir şekilde daha düşük olan bir akciğer V20 değerlerini bulduklarını belirtmişlerdir [6].

Bulgular ışığında akciğer dozları, IMRT tekniklerinde 3DCRT tekniğine göre daha avantajlı gözükmektedir.

Travis ve ark. 105 meme kanseri olgusu ve 266 eşleştirilmiş kontrolden oluşan büyük ve uluslararası vaka kontrol çalışmasında, memeye, 4 Gy veya daha düşük radyasyon dozu alan ve alkilleyici kemoterapi almayan kadınlara kıyasla 3,2 kat meme kanseri riski ile ilişkilendirmişlerdir. Memeye 40 Gy ve üzerinde doz alan kadınlarda ise, riskin sekiz kat arttığı bildirilmiştir (p <0. 001) [13].

Nieder ve ark. ları. mediastinal HL'lı sekiz kadın hastada yaptığı çalışmada ise, IMRT ile ortanca kalp ve meme dozlarını belirgin daha düşük bulmuşlardır. Bununla birlikte, artan meme hacimleri, IMRT kullanılarak, düşük (%15 veya daha az) dozlar almıştır [14].

Bazı radyasyon onkologları, hodgkin lenfomalı kadın hastalarda IMRT kullanmakta isteksizdirler çünkü; normal yapıların yüksek doza maruz kalması ve meme gibi büyük normal dokuların, aşırı düşük doz radyasyona maruz kalması konusunda endişeleri vardır. Meme kanseri riski açıkça doza bağımlı olsa da, düşük doz radyasyon ve karsinojenez arasındaki ilişkinin daha spekülatif olduğunu bildirmişlerdir [15,16]. Weber ve ark. ları. IMRT'yi konvansiyonel tekniklerle karşılaştırmak için nonlinear bir doz risk modeli kullanmışlardır. IMRT' yi diğer konformal tekniklerle karşılaştırdıklarında, radyasyona bağlı kanser riskini tahmini artırabileceği sonucuna varmışlardır [17].

Fiandra ve ark. larının yaptığı çalışmada ise, butterfy VMAT'ta, meme mean dozları diğer tedavi planlarıyla kıyaslandığında istatistiksel olarak anlamlı düşük bulunmuştur [11].

Çalışmamızda ise sağ meme mean, V5, V20 ve sol meme mean ve V5 değerleri 3DCRT planlama için daha düşük değerlerle daha avantajlı ve istatistiksel olarak anlamlı bulundu. Sağ meme maksimum, V25, V30 ve sol meme maksimum, V20, 25, 30 değerleri ise 3DCRT planlamada diğer VMAT planlarında elde edilen değerlerden daha yüksektir bu da istatistiksel olarak anlamlı bulundu.

HL tedavisi sonrası kardiyak mortaliteye ek olarak, kardiyak morbidite de tanımlanmıştır. Florida Üniversitesi'nde, 415 HL RT öyküsü olan hasta üzerinde yapılan retrospektif bir çalışmada, %10,4 olguda koroner arter hastalığı geliştiği bildirilmiştir. Çok değişkenli analizde, koroner arter hastalığı riski ile anlamlı şekilde ilişkili olan tedaviye bağlı tek risk faktörü bulunmuştur. Bu, tek başına mantle veya subdiyafragmatik tedavi ile karşılaştırıldığında, mantle ve para-aortik alanın birlikte kullanılması olarak bildirilmiştir [18].

Son yıllarda, radyoterapi alanı, mevcut yan etkilerden dolayı genişletilmiş alandan tutulu alana düşürülmüştür ISRT tedavisi, RT tekniklerindeki diğer son gelişmelerle, kritik organların aldığı dozu sınırlarken, öngörülen dozu hedef volüme IMRT tekniği ile vermeyi içermektedir [19]. Ek olarak, özellikle mediastinal yapılar için önemli olan nefes tutma tekniğinin kullanılması, hedef kitleye doz dağılımını daha iyi sağlar [20]. Kardiyak komplikasyon riskinin de azaltılabilineceği bildirilmiştir.

Fiandra ve ark. ları yaptıkları çalışmada ise kalp mean dozlarını tüm planlama tekniklerinde benzer bulmuşlardır [11]. Biz de çalışmamızda, LAD ve kalp dozlarını VMAT tekniklerinde daha düşük bulduk.

Constine ve arkadaşlarının HL hastalarında yaptıkları bir çalışmada, 26 Gy veya daha yüksek doz alan çocukların %78'inde, 26 Gy veya daha düşük doz alan çocuklarda ise yalnızca %17'sinde tiroid anormalliklerinin geliştiğini bildirmişlerdir [21]. Çocukluk Çağı Kanserinde Hayatta Kalma Araştırması Sonuçları, HL'den kurtulanların kardeş kohortuna kıyasla 17 kat artmış hipotiroidizm riski gösterdiğini bildirmişlerdir [22].

Fiandra ve ark. ları troid mean dozlarını, 3DCRT'ye göre, VMAT ve butterfly-VMAT'ta daha düşük bulmuşlardır [11]. Bizde kliniğimizde tiroid dozlarımızı, VMAT planlarımızda daha düşük bulduk. VMAT planında ise, butterfly VMAT'a göre daha düşük dozlar bulundu.

Imanimoghaddam ve ark. ları servikal, supra ve infraklavikular HL nedeniyle RT alan çocuklarda, baş-boyun tümörlü yetişkin

RT alan hastalarla benzer tükrük bezi değişimleri olduğunu bildirilmişlerdir. Gözlenen hiposalivasyon ve kserostominin hastanın yaşam kalitesinin etkilediğini savunmuşlardır [23]. RT ayrıca, doku inflamasyonu nedeniyle; laktoferrin, lizozim ve immünglobulin gibi protein paternlerinin seviyelerini arttırdığını α-amilaz aktivite ve konsantrasyonunu azaltıp, müsin konsantrasyonunu düşürdüğünü bildirmişlerdir [24]. Tükrükteki bu değişimler ise hastaları lokal enfeksiyonlara daha savunmasız yapacağını belirtmişlerdir [25].

Bizde kliniğimizde sağ ve sol parotis mean, V5,20 25, 30 değerlerini, Butterfyl VMAT planlamada diğer planlara göre istatistiksel olarak anlamlı düşük dozlar bulduk. Sağ parotis V20 değeri ikili karşılaştımalarda ise; butterfl VMAT planlamada, VMAT plana göre daha düşük bulundu ve istatistiksel olarak anlamlı kabul edildi. Sağ parotis V25 ise butterfly VMAT planlamada, VMAT plana göre daha düşük bulundu ancak istatistiksel anlamlı değildi. Butterfl VMAT planlamada parotis dozlarının, daha avantajlı olduğu kanaatine varıldı.

Literatürde, boyun ve mediasten tutulumu olan HL tanılı hastalarda, Butterfly VMAT ve VMAT planlarının parotis açısından karşılaştırmalı bir çalışmaya ulaşılamadı. Biz çalışmamızda literatürde ilk olabilecek, parotis dozlarını, bu iki planlama tekniğini ile karşılaştırmaktayız. Çalışmamızdaki kısıtlama, hasta sayısının sınırlı olmasıydı. Daha fazla hasta sayısıyla değerlendirilmesini önermekteyiz.

Sonuç

Bu sonuçlar ışığında, kritik organ dozları incelendiğinde memede 20 Gy ve üzerinde VMAT, butterfly VMAT, 20 Gy ve altında ise 3DCRT tekniğinin daha avantajlı olduğu görülmektedir. Bu çalışma sonucunda kadın ve çocuk hastalarda ikincil kanser oluşma riski endişesiyle 3DCRT kullanılması gerekmektedir. Parotis dozları açısından ise butterfly VMAT'ın daha avantajlı olduğu görülmektedir. Yetişkin erkek hastalarda ise, VMAT, butterfly VMAT tedavi planlarının kullanılmasının daha uygun olacağı kanaatine varılmıştır. RT planlaması, otomatik olmamalı ve tedavi planı, her hastaya en uygun şekilde bireysel olarak özenle seçilmelidir.

Maddi Destek ve Çıkar İlişkisi

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur.

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Turkish Journal of Clinics and Laboratory

To cite this article: Kilic A, Baydar O. Monocyte to high-density lipoprotein ratio and high sensitive c-reactive protein levels in patients with isolated coronary artery ectasia. Turk J Clin Lab 2020; 4: 282-287.

Original Article

Monocyte to high-density lipoprotein ratio and high sensitive c-reactive protein levels in patients with isolated coronary artery ectasia

Monosit yüksek/ dansiteli lipoprotein oranı ve yüksek sensiviteli c- reaktif protein değelerinin izole koroner arter ektazisi ile ilişkisi

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Abstract

Aim: Isolated coronary artery ectasia (ICAE) is a rare form of coronary artery disease and has almost same mortality and morbidity rate to atherosclerotic coronary artery disease. Monocyte to HDL-cholesterol ratio (MHR) has been entered the literature as a new inflammatory indicator in various cardiovascular disease. In this study we want to investigate relationship between inflammatory and oxidative markers that high sensitive C reactive protein (Hs-Crp), MHR and ICAE.

Material and Methods: We retrospectively observed patients who underwent elective coronary angiography. Patients with ICAE and normal coronary arteries included in the study. MHR and Hs-Crp levels were observed just before the coronary angiography procedure.

Results: A total of 98 patients (61, 62 % men) patients were included in this study and 28 (28.6%) of them had DM. 68 (69.3%) of patients had ICAE. MHR was significantly higher in patients with ICAE (0.0153 (0.007-0.130)ve 0.0111 (0.005-0.020), p< 0.001). Hs-Crp was also significantly higher in patients with ICAE (Yd-Crp: 6 (0.2-33)ve 1(0.2-14), p < 0.001). MHR was also significantly correlated with Hs-crp levels (r:0,338, p: 0.001). Additionally; DM, smoking, HT, MHR and Hs-crp were detected as independent risk factors of ICAE in logistic regression analysis. In receiver operating characteristic curve analysis, the area under the curve for predicting CAE was 0.744 (p<0,001, 95% confidence interval [CI] 0.64 to 0.84) and cut- off value was 0.013 (sensitivity 69.1%, specificity 63.3%,) for the number of MHR.

Conclusion: MHO and Hs-Crp are markers of inflammation that can be easily and inexpensively examined and found high in patients with ICAE. These markers may be useful explaining the pathogenesis of ICAE and guiding treatment.

Keywords: coronary ectasia; monocyte to high-density lipoprotein ratio; high sensitive c reactive protein

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Recevied: 06.03.2020 accepted: 24.08.2020
Doi: 10.18663/tjcl.699728

Öz

Amaç: Izole koroner arter ektazisi (İKAE), koroner arter hastalığının az görülen bir formu olup, aterosklerotik koroner arter hastalığna benzer mortalite ve morbidite oranına sahiptir. Monosit yüksek dansiteli lipoprotein (HDL) oranı (MHO) klinikte yeni tanımlanan inflamasyon belirteçlerinden biridir. Çalışamızda MHO ve klinikte inflamasyon belirteci olarak sıkça kullanılan yüksek duyarlıklı C-reaktif protein (Yd-Crp) ile İKAE arasıdaki ilişki araştırılmıştır.

Gereç ve Yöntemler: Çalışmamızda retrospektif olarak elektif koroner yapılan hastalar incelenmiştir. Hastaneye başvuruşunda koroner anjiografi hemen öncesinde alınan örneklerden Yd-Crp ve MHO oranı hesaplanmıştır.

Bulgular: Toplam 98 (61, %62 erkek) hasta geriye dönük incelenmiş, 28 (%28.6) hastada Diabetes Mellitus saptamıştır. İKAE hasta sayısı 68 (%69.8) olarak bulunmuştur. MHO ve Yd-Crp ; İKAE grubunda normal koroner arterlere sahip gruba göre anlamlı olarak yüksek saptandı (Sırasıyla; MHO: 0.0153 (0.007-0.130)ve 0.0111 (0.005-0.020), p< 0.001, Yd-Crp: 6 (0.2-33)ve 1(0.2-14), p < 0.001). Ek olarak MHO ile Yd- Crp değeri arasında pozitif korelasyon saptandı (r:0,338, p: 0.001). Ayrıca; hipertansiyon , Diabetes Mellitus, sigara kullanımı, Yd-Crp ve MHO değerleri İKAE' nin bağımsız risk faktörleri olarak bulundu. ROC analizinde MHO için eğri altında kalan alan 0.744 (p<0,001, 95% [CI] 0.64 - 0.84) ve cut- off değeri 0.013 (%69.1 sensivite , % 63.3 spesifite) saptandı.

Sonuç: Sonuç olarak MHO ve Hs-Crp basit ve ucuz şekilde bakılabilen inflamasyon belirteçleri olup, İKAE hastalarında yüksek saptanmıştır. Bu beliteçler, İKAE hastalığının patogenezinin aydınlatılmasında ve tedavinin yönlendirilmesinde faydalı olabilir.

Anahtar Kelimeler: koroner arter ektazisi; monosit yüksek dansiteli lipoprotein (hdl) oranı; yüksek duyarlılıklı c- reaktif protein.

Introduction

Isolated coronary artery ectasia (ICAE) is a rare coronary anomaly and commonly accepted to be a different form of coronary artery disease (CAD). ICAE may be asymptomatic in cases without obstructive CAD, but it can show up with coronary ischemia signs.[1] Monocytes are one of important mononuclear cells that develop in the bone marrow and circulate within the bloodstream. Monocytes are special cell types for secretion of inflammatory cytokines. These cells are important during the early stages of atherosclerosis and the local proliferation that is responsible for atherosclerotic progression. Thus, monocytes have an important role in early stage lesions and in the chronic stages of the disease. [2] Additionally, high-density lipoproteincholesterol (HDL-C) protects endothelial cells against the atherogenic effects of low-density lipoprotein cholesterol (LDL-C) and inflammatory cells. [3-5] This effects reverse atherosclerosis progress. So, HDL-C has very important role in anti-inflammatory actions. Monocyte to HDL-cholesterol ratio (MHR) and High sensitive C- reactive protein (Hs-Crp) are very considerable inflammatory markers and several studies have shown that strong correlation between various cardiovascular diseases.[6-8] Because of inflammation is the main cause of ICAE; increased MHR and Hs-Crp may be associated with pathogenesis of ICAE. In the literature, there is not enough studies about MHR in patients with ICAE. Although the relationship between the risk of developing CAE and MHR was demonstrated [9], there is a relationship between MHR and Hs-Crp in the patient with ICAE is still unclear. Thus, the aim of this study was to assess whether there is a relationship MHR and Hs-Crp in patients with ICAE.

Material and Methods

Study population

Total of 98 consecutive patients with ICAE undergoing coronary angiography were retrospectively enrolled in our study, between February 2014 and December 2017. Patients with cardiopulmonary arrest, active infection, systemic inflammatory disease, contrast medium administration within 15 days, chronic renal failure (serum creatinine >2 mg/dl), end-stage liver disease, malignancy and using lipid-lowering drugs were excluded from the study. We also excluded patients with left ven-tricular ejection fraction [LVEF]<50%, percutaneous coronary intervention and coronary artery bypass grafting history. ICAE which is not accompanied by a significant coronary artery stenosis described as dilatation of at least one coronary artery so as to be 1.5-fold or greater than the normal coronary artery segment and (1). Diabetes mellitus (DM) was described by fasting serum glucose levels of at least 126 mg/ dl, a random plasma glucose level of >200 mg/dl and/

or if the patient was taking oral anti-diabetic drugs, or insulin. Hypertension (HT) was described as a systolic blood pressure > 130 mmHg and/or a diastolic blood pressure > 80 mmHg or treatment with any antihypertensive drugs. Hyperlipidemia (HL) was described as a total cholesterol greater than 200 mg/dl and/or a low-density lipoprotein cholesterol (LDL) level greater than 130 mg/dl or previously treated HL. Current smokers are described who have smoked regularly in the previous 6 months. A family history of coronary artery disease was defined as a coronary event occurring in men before 55 years old or a coronary event occurring in women before 65 years of age. The hospital local ethics committee approved our study. Our study was performed in accordance with the Helsinki Declaration.

Coronary angiography and intervention

Coronary angiography was performed according to clinical indications (Stress echo, treadmill test, myocardial perfusion scintigraphy or typical chest pain). Coronary angiography (CA) (Siemens Axiom Artis zee 2006; Germany) was performed by femoral or radial approach according to standard practice. We performed echocardiography (Philips Epiq 7, Medical System) to all patients during hospitalization. The left ventricular systolic performance was calculated using the modified Simpson's method.

Laboratory analysis

Complete blood count (CBC) and cholesterol levels were measured at the time of admission. For definition of CIN, serum creatinine levels were measured before and after procedure. CBC levels were observed using Cell-Dyn 3700 (MAPSS Laser Differential; Abbott Laboratories, USA). Cholesterol levels that total cholesterol, HDL-C and triglyceride, were observed enzymatically (Hitachi 7350 autoanalyzer, Hitachi Ltd, Japan). Additionally, LDL-C levels were measured with Friedewald formula. MHR was calculated by dividing monocyte count (109/L) to HDL-C level (mmol/L). The estimated glomerular filtration rate (eGFR) was measured using the Modification of Diet in Renal Disease formula [20]. High-sensitivity C-reactiveprotein (hsCRP) was measured by using Beckman Coulter analyzer before the coronary angiography.

Statistical analysis

Statictical analyses were observed using SPSS version 22.0 package program (SPSS Inc, Chicago, Illinois). Kolmogorov Smirnov testing was used to determine the subjects' distribution. Normally distributed variables are presented as mean ± standard deviation (SD) and not normally disturbed subjects were showed median and quartile range. The independent samples t test was used to compare the values and nonparametric values were compared using the Mann-Whitney U test. Chi-square test were performed for comparison of categorical variables. To evaluate the effects of various factors on ICAE development, regression analyses using the backward Logistic Reggression (LR) method were performed. Variables for which the P value of <0 .05 was considered significant. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off values to predict the development of ICAE.

Results

A total of 98 patients (61, 62 % men) patients were included in this study and 28 (28.6%) of them had DM. 68 (69.3%) of patients had ICAE. MHR was significantly higher in patients with ICAE (0.017± 0.0014 vs 0.011± 0.003, p: 0.033). Hs-Crp was also significantly higher in patients with CAE (7.2± 4.4 vs 1.6± 2.6, p < 0.001). Weight, age and males were significantly higher in patients with CAE. Also, general risk factors that HL, smoking and HT were significantly higher in patients with ICAE. Previous medications, HbA1c, DM rates were not differed between two groups. The baseline clinical characteristics of patients were shown in Table 1 and 2. MHR was also significantly correlated with Hs-crp levels (r:0,338, p: 0.001). Additionally; DM, smoking, HT, MHR and Hs-crp were detected as independent risk factors of ICAE in logistic regression analysis (Table 3). In ROC curve analysis, the area under the curve for predicting CAE was 0.744 (p<0,001, 95% confidence interval [CI] 0.64 to 0.84) and cut- off value was 0.013 (sensitivity 69.1%, specificity 63.3%,) for the number of MHR (Table 4) (Figure 1).

Table 1. Main Characteristics of Patients

	Patients with CAE (n:68)	Patients without CAE (n:30)	P
Age (year)	63.0± 10.8	54.2± 9.9	<0.001
Men (n%)	48 (70.6%)	13(43.3%)	0.010
BMI (kg/m2)	29.6±5.5	31.9±6.2	0.077^
HT (n%)	52(76.5%)	15 (50.0%)	0.009
HL (n%)	42 (61.8 %)	8 (26.7%)	0.001
DM (n%)	17 (25.0 %)	11(36.7 %)	0.23
Smoker (n%)	39 (57.4%)	9(30.0%)	0.013
EF(n%)	60(20-60)	60(60-60)	<0.001*

HT: Hypertension, DM: Diabetes Mellitus, HL: Hyperlipidemia, EF: Ejection fraction, CABG: Coronary artery bypass grefting, BMI: Body mass index. *: Mann-Whitney U test , ^: Independent samples t test

Table 2. In-hospital clinical course of Patients

	Patients with CAE N: 68	Patients without CAE N:30	p
MHR	0.0153 (0.007-0.130)	0.0111 (0.005-0.020)	<0.001*
WBC	7.7±2.1	7.6±1.9	0.79^
HGB	13.4±1.6	12.8±1.6	0.13^
PLT	250.7±66.7	246.1±82.9	0.77^
NEU	4.8±2.0	5.0±1.9	0.72^
LYM	2.0±0.6	1.8±0.7	0.23^
MON	0.6±0.5	0.6±0.1	0.67^
HDL	37(26-44)	52 (43-63)	<0.001*
LDL	120.4±31.8	120.7±42.2	0.97^
TG	121(46-480)	144(44-437)	0.12*
NON HDL	157.1±34.9	150.2±50.1	0.010^
Glucose (mg/dl)	104 (59-321)	105 (79-284)	0.57*
HBA1C (%)	5.7±0.6	5.5±0.6	0.80^
Creatinine (mg/dl)	0.96 (0.55-2.24)	0.98 (0.57-1.99)	0.89*
Hs-Crp	6 (0.2-33)	1(0.2-14)	<0.001*
Uric Acid	5.6±1.6	6.0±2.5	0.011^

MHR: Monocyte HDL ratio, Hs-Crp: High sensitive Crp, *: Mann-Whitney U test , ^: Independent samples t test

Table 3. Independent risk factors of CAE in logistic regression analysis

Variables	OR (95% C.I)	P
Age	1.1 (0.9-1.3)	0.019
MHR	0.70(0.5-0.9)	0.006
Smoke	0.77(0.60-0.98)	0.038
Hs-Crp	0.9(0.7-1.2)	0.003
Gender	1.6 (0.7-3.8)	0.032
DM	0.6 (0.4-1.3)	0.020
HT	0.6 (0.5-0.8)	0.015

HT: Hypertension, DM: Diabetes Mellitus, BMI: Body mass index , MHR: Monocyte to HDL ratio, Hs-Crp: High sensitive Crp

Table 4. Receiver operating characteristic (ROC) curve analysis

	Area	Std. Error	Asym. Sig.	Confidence interval
MHR	0.744	0.051	<0.001	0.6-0.8

MHR: Monocyte to HDL ratio,

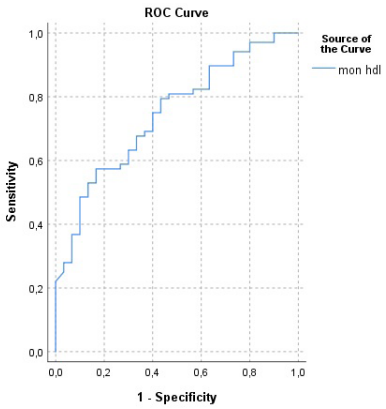

Figure 1: Receiver operating characteristic (ROC) curve analysis.

Discussion

ICAE is rare situation that may be congenital or acquired and its common aetiologies are 50% atherosclerosis, 20-30% congenital diseases, and 10-20% inflammatory or connective tissue diseases.[10-12] ICAE is very rare and mostly asymptomatic. Symptomatic cases usually suffer form of effort angina. However, it may also manifest itself with unstable angina. Reduced coronary flow due to microvascular dysfunction has been demonstrated to be responsible for ischemia in cases that have not stenotic CAD. Some publications reported that ectasia caused slow flow, thrombus formation and vasospasm in coronary arteries, also lead to myocardial infarction without obstructive CAD.[12,13] Current studies showed that inflammatory processes has a great role in the aetiopathogenesis of ICAE and also a previous study revealed that damage of the vascular media layer as the cause of this pathology.[14] Therefore, inflammatory cells can be detected in this vascular layers.[15]

Blood cell derived tests are an easy and effective methods to observe the systemic inflammation in various diseases. Recents studies have presented that elevated systemic inflammatory markers have been linked to various cardiovasculary pathologies. Monocyte cell which is a one of leukocyte type have an important role during inflammatory process and its activation plays a key role in cardiovascular diseases.[15,16] The most important cause of atherosclerosis is considered inflammation, so monocytes share in the onset and progression of atherosclerosis.

HDL-C particles block macrophage cell activation and remove cholesterol particles from endothelium.[17] These molecules

provide anti-inflammatory effects. The monocyte chemotaxis reveals an inflammatory and toxic effect, but HDL-C molecules have preventive functions during this pathological process. Therefore, the ratio of two parameters can provide important information about the inflammatory state. MHR is a novel marker that gives important information about inflammation. Although the relationship between the risk of developing CAE and MHR was demonstrated [9], the role of MHR was lessknown during development of ICAE. Therefore, we hypothesized that an increased MHR may explain pathophysiology and be an early predictor of ICAE. Recent studies showed that increased MHR was an independent risk factor of major cardiovascular events in patients with chronic kidney disease and atrial fibrillation recurrence after cryoballoon.[15,16,18-22]. In our study, we observed that patients with ICAE have significantly higher MHR and Hs-Crp levels compared to control group and our findings also indicated that an MHR and Hs- Crp were significantly independent risk factor of ICAE. MHR has a strong positive correlation with serum hs-CRP level, which supports its important role in systemic inflamation. For this results, MHR may gain a critical role for prediction of ICAE during diagnostics follow-up.

Other risk factors that smoking, HT and DM are common in patients with coronary artery disease and comorbid ICAE in previous studies.[11] Our study suggested these results that DM, smoking, HT and Hs-crp were detected as independent risk factors of ICAE.

Our study has several limitations. First, it is retrospective and a single-center study. Second, we used a single MHR value before the procedure. Another limitation is that the visual observation of coronary angiography was only performed. Finally, the number of patients were relatively small and we did not follow- up patients for futher evaluation.

Conclusion

MHO and Hs-Crp are markers of inflammation that can be easily and inexpensively examined and found high in patients with ICAE. These markers may be useful explaining the pathogenesis of ICAE and guiding treatment.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Turkish Journal of Clinics and Laboratory

To cite this article: Tumer NB. N-acetyl cysteine attenuates ferroptosis mediated lung injury induced by lower limb ischaemia/reperfusion.Turk J Clin Lab 2020; 4: 288-293.

Original Article

N-acetyl cysteine attenuates ferroptosis mediated lung injury induced by lower limb ischaemia/reperfusion

N-asetil sistein alt ekstremite iskemi/ reperfüzyonu tarafından indüklenen feroptosise bağlı akciğer hasarını azaltır

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Abstract

Aim: This study aimed to analyze the effect of N-acetyl cysteine pretreatment on the prevention of ferroptosis mediated lung injury induced by lower limb ischemia and reperfusion.

Material and Methods: Eighteen male Sprague-Dawley rats weighing 350-400 g were randomized into three groups. The animals received N-acetyl cysteine 150 mg/kg or normal saline 0.1 ml/kg intraperitoneally before the ischemic period. In the control and study groups, I/R injury was induced by clamping the aorta infrarenal for 2 hours, followed by 4 hours of reperfusion. The third group underwent sham surgery. After sacrifice, the lungs of the animals were extracted for both histopathological and biochemical analysis.

Results: There was a significant difference between the control and study animals regarding tissue malondialdehyde (MDA), and glutathione (GSH) levels. In the control group, the MDA levels were increased and the GSH levels were increased significantly compared to the sham group that revealed a ferroptosis mediated lung injury. However, N-acetyl cysteine decreased the levels of MDA and increased the levels of GSH revealing a protective effect. The Prussian blue (free iron stain) staining which was used to examine iron deposition revealed a reduced deposition of iron in the N-acetyl cysteine group.

Conclusion: The results of the present study suggest a protective effect of N-acetyl cysteine on ferroptosis mediated lung injury induced by lower limb ischemia-reperfusion in a rat model.

Keywords: Feroptosis; ischemia/reperfusion; n-acetyl cysteine

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Recevied: 15.07.2020 accepted: 11.08.2020
Doi: 10.18663/tjcl.769961

Öz

Amaç: Bu çalışma, N-asetil sistein ön tedavisinin, alt ekstremite iskemisi ve reperfüzyonun neden olduğu ferroptoza bağlı akciğer hasarının önlenmesi üzerindeki etkisini analiz etmeyi amaçlamıştır.

Gereç ve Yöntemler: 350-400 g ağırlığında on sekiz erkek Sprague-Dawley sıçanı üç gruba randomize edildi. İskemik dönemden önce intraperitonal olarak 150 mg / kg N-Asetil Sistein veya normal salin 0.1 ml / kg verildi. Kontrol ve çalışma gruplarında, aort infrarenal düzeyde klemlenerek 2 saat boyunca I/R ve sonrasında 4 saat reperfüzyon indüklendi. Üçüncü gruba sham grubu olarak kullanıldı. Hayvanlarının hayatı sonlandırıldıktan sonra, histopatolojik ve biyokimyasal analiz için akciğerleri çıkarıldı.

Bulgular: Doku Malondialdehit (MDA) ve glutatyon (GSH) seviyeleri arasında istatistiksel olarak anlamlı fark tespit edildi. Kontrol grubunda, MDA düzeyleri ve GSH düzeyleri, ferroptoza bağlı akciğer hasarı gösteren sham grubuna kıyasla önemli ölçüde arttı. Bununla birlikte, NAC alan grupta MDA seviyesi düşerken koruyucu bir etki olarak GSH seviyeleri yükseldi. Demir birikimini göstermek için kullanılan Prusya mavisi (serbest demir lekesi) boyaması, N-asetil sistein grubunda demir birikiminin azaldığını ortaya çıkarmıştır.

Sonuç: Bu çalışmanın sonuçunda, bir sıçan modelinde alt ekstremite iskemisi-reperfüzyonunun neden olduğu ferroptozise bağlı akciğer hasarı üzerine N-asetil sisteinin koruyucu bir etkisi olduğunu düşündürmektedir.

Anahtar kelimeler: Feroptozis; iskemi/reperfüzyon; n-asetil sistein

Introduction

Lower limb ischemia/reperfusion (I/R) is an important and common event in clinical practice. Reperfusion results in both local and systemic damage, in part through rapid oxygen free radical generation and inflammatory mediators [1,2]. Reactive oxygen species (ROS) have a destructive role in mediating tissue damage during I/R injury. Once the reestablishment of blood flow to the ischaemic tissue is provided, an influx of molecular oxygen catalyzes xanthine oxidase to degrade hypoxanthine to uric acid and thereby liberating the highly reactive superoxide anion (O2-). Superoxide is then converted to hydrogen peroxide (H2O2) and the hydroxyl radical (OH•). The major consequence of hydroxyl radical production is peroxidation of the lipid structures of cell membranes resulting in cell death [2]. Remote organ damage after I/R mainly occurs in the lungs, kidneys, and heart.

Ferroptosis is a form of regulated cell death identified as iron-dependent, nonapoptotic cell death. In addition to iron accumulation, there is also an accumulation of lipid peroxidation products in this type of cell death [3]. In ferroptosis, there is also depletion of glutathione (GSH) or the inactivation of the lipid repair enzyme GSH peroxidase 4 (GPx4) [4]. The major factor that triggers ferroptosis is ROS accumulation [5]. Ferroptosis has been reported to be involved in many pathophysiological situations such as myocardial infarction, degenerative diseases, neurological diseases, antiviral immunity, cancer, and I/R injury [6-9]. It is reported that inhibition of ferroptosis alleviated I/R induced acute lung injury [9,10].

N-acetylcysteine (NAC) is a sulfhydryl group transmitter. It is used primarily in the treatment of paracetamol overdose [11]. It is a strong antioxidant, mucolytic and has anti-inflammatory effects. NAC as an antioxidant directly scavenges ROS through its thiol groups and increases intracellular glutathione levels [12].

Therefore, this study aimed to analyze the effect of NAC pretreatment on the prevention of ferroptosis mediated lung injury induced by lower limb ischemia and reperfusion.

Materials and Methods

This study was approved by the Institution of Animal Care and Use Committee and complied with the Guide for the Care and Use of Laboratory Animals. (IRB No: 66332047-604.01.02) Eighteen male Sprague-Dawley rats weighing 350-400 g were randomized into three groups. The animals were initially anesthetized with intraperitoneal ketamine hydrochloride (Ketalar; Pfizer, Ortakoy, Istanbul, Turkey) 100 mg/kg body weight. The abdomen was then explored through a midline incision after shaving and disinfection. In the sham group (Group I), laparotomy was performed. In the control group and the study groups, I/R injury was induced by clamping the aorta with atraumatic vascular clamp infrarenal for 2 hours, followed by 4 hours of reperfusion. Cessation of arterial flow

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was confirmed using the absence of an audible continuous-wave Doppler signal. Study group animals (Group II) received NAC 150 mg/kg and control group animals (Group III) received normal saline 0.1 ml/kg intraperitoneally before the ischemic period. At the end of these procedures, the animals were sacrificed with the lethal injection of sodium thiopental (Pentothal Sodium, Abbot, Italy). Immediately after sacrifice, through midline sternotomy, lungs were extracted and washed with 0.9% saline solution for both histopathological (hematoxylin-eosin staining) and Prussian blue staining (free iron stain, Sigma-Aldrich) to examine iron deposition and biochemical analysis (malondealdehyde assay (MDA) and total glutathione (GSH) assays).

Wet-to-dry lung weight ratio

Wet-to-dry lung weight ratio (W/D) is an index of pulmonary edema. The left lower lung was excised and weighed immediately (wet weight). The lung tissue was then dried in an oven for 5 days at 60°C and reweighed (dry weight). The W/D was calculated by dividing the wet weight by the dry weight, as described previously [13].

Biochemical Analysis

Lung tissues were frozen immediately in liquid nitrogen and stored at -80°C until measurements were done. We prepared 20-µm-thick sections, which were dried under vacuum overnight at 20°C. The dried-frozen sections were stored at -20°C until biochemical assays were done.

The determination of MDA and total GSH were performed by enzyme-linked immunosorbent (ELISA) assay. The levels of MDA in lung tissue were measured based on the Biotin double antibody sandwich technology (Bioassay Technology Laboratory, Shangai, China). MDA concentration was expressed as nmol/ml (level of detection (LOD): 0.024 nmol/ml, level of quantification (LOQ): 10 nmol/ml). Total GSH levels in the lung tissue were determined according to Ellman in nmol/mg [14].

Histopathological examination

Tissue samples were fixed in 10% formalin and embedded in paraffin with routine follow-up procedure; 4-5 µm sections were cut from paraffin blocks and stained with hematoxylin and eosin (H-E) and Prussian blue for light microscopic examination (x200). A histopathologist unaware of the groups assigned a score of 0–4 to each section as follows: 0, normal histologic appearance; 1, vascular congestion; 2, vascular congestion and interstitial edema; 3, alveolar structural disturbance and infiltration of inflammatory cells; 4, massive alveolar structural disturbance and infiltration of inflammatory cells [15]. Prussian blue staining is widely used for the assessment of iron deposition in tissues. After deparaffinization and rehydration, the lung sections were treated with a 20% hydrochloric acid solution to liberate ferric iron and then treated with a 10% aqueous potassium ferrocyanide solution to produce insoluble ferric ferrocyanide. After this procedure, the sections were counterstained with eosin. This staining identifies ferric iron as bright blue and nuclei as red [16].

Statistical analysis

Statistical analyses were performed using SPSS 18 (IBM Corp, New York, USA). Values are expressed as mean±SD. The difference between the groups was analyzed either with unpaired

Student's t-test or one-way ANOVA with Bonferroni's correction. p-Values of less than 0.05 were considered significant.

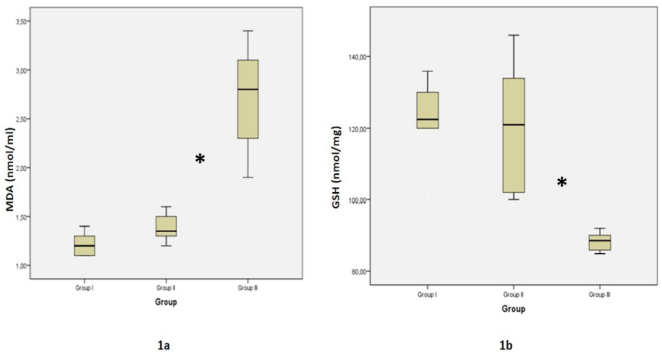


Figure 1. A: Malondialdehyde (MDA) production was reduced in NAC pretreated lung tissues (Group II) compared with that of the control group (Group III). B: Total GSH levels were increased in the NAC group. Group I: Sham group. Data are presented as medians with total range. *p<0.05 Group II vs Group III.

Results

Biochemical assay results

MDA was studied here as a marker of free radical-mediated lipid peroxidation. In the control group animals, the tissue MDA levels were increased significantly compared to the sham group that revealed a ferroptosis mediated lung injury (2.72±0.56 and 1.22±0.12 respectively, p< 0.001). Animals that received NAC showed a general trend of less lipid peroxidation product in lung tissue than the control group and this decrease was statistically significant (Figure 1a). Tissue MDA levels

significantly decreased in NAC received animals compared to the control group (1.38±0.15 and 2.72±0.56 respectively, p<0.001). N-acetyl cysteine pretreatment increased the tissue levels of GSH compared to the control group revealing a protective effect (120.67±19.17 and 88.33±2.58 respectively, p=0.002, Figure 1b).

Weight to dry ratio results

A higher W/D was noted after IR. The NAC pretreatment group had lower W/D (Figure 2).

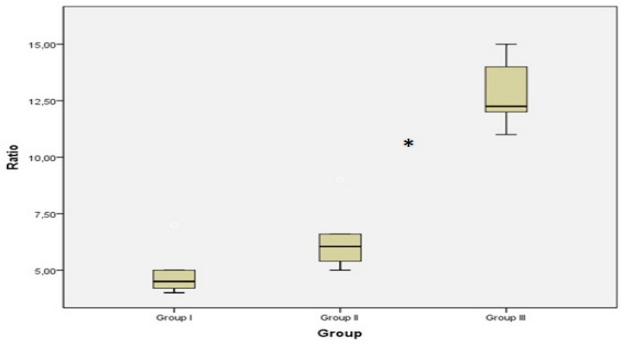


Figure 2. Lung wet-to-dry weight ratio. Edema formation (wet/dry weight) in lung tissue increased following lower extremity ischemia-reperfusion. Data are presented as medians with total range. *p < 0.05 Group II vs Group III. Group I: sham, Group II: NAC pretreatment, and Group III: control.

Histopathological examination results

Hemotoxylin and eosin staining examination showed normal lung architecture and arrangement in the sham group. The histological structure of pulmonary interstitial tissue and alveolus was intact and visible in the sham group by light microscopy, without infiltration of inflammatory cells stained with H-E (Figure 3a). Obvious histological changes were observed in the control group (Figure 3b) compared to the sham group: atelectasis, thickening of alveolar inter wall, infiltration of inflammatory cells. Histological changes decreased in the study group pretreated with NAC compared to the control group; NAC pretreatment protected against I/R induced injury, with approximately normal lung architecture in lung sections with the normal structure of pulmonary interstitial tissue and alveolus, and less infiltration of inflammatory cells (Figure 3c). In the control group, lung injury was significantly higher than the sham and NAC pretreatment groups (p<0.001; Figure 4). These results indicated that lung injury score was significantly increased by IR, whereas NAC pretreatment significantly decreased lung injury score (Figure 4). The Prussian blue staining which was used to examine iron deposition revealed no or very little amount of detectable iron in sham group lung sections (Figure 3d). However, intense blue positive staining was consistently observed in sections from control animals (Figure 3e), whereas the amount of stainable iron was significantly reduced in NAC pretreated animals (Figure 3f).

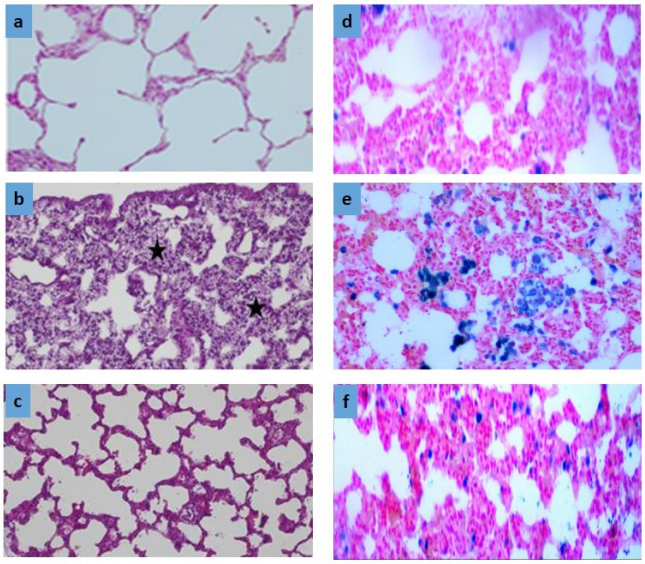
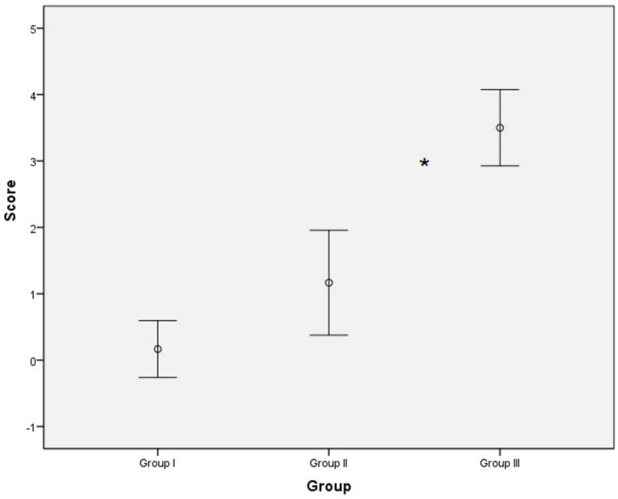


Figure 3. H&E and Prussian blue staining of lung tissues. Magnification: x100 or x200. Scale bar, 50 µm or 100 µm. a,d: sham, b,e: control, c,f: NAC pretreated rat lung tissue specimens.



Discussion

Ischemia/reperfusion injury is a common situation in both cardiac and peripheral arterial surgical procedures. The main injury occurs during the reperfusion period of the ischemic tissue in I/R and leads to cellular damage and organ dysfunction ultimately [17]. Remote organ damage is

another consequence of I/R injury. Cellular hypoxia results in decreased ATP production disrupts ion pump function and a shift to anaerobic glycolysis for energy production ensues. Activation of ROS is initiated during ischemia and during reperfusion period, a burst of ROS generation occurs which ultimately results in the respiratory burst of superoxide production, and thus massive oxidative stress is intensified that directly damages cells and induces both the programmed cell death responses, apoptosis and necroptosis and also a non-apoptotic cell death known as ferroptosis [18-20].

In this study, we aimed to show the effect of NAC pretreatment on the prevention of ferroptosis mediated lung injury induced by lower limb ischemia and reperfusion in a rat model. The present research found typical ferroptotic biochemical changes in control group animals as GSH depletion with increased tissue MDA levels meaning increased lipid peroxidation. However, NAC pretreatment is reported to be protective against remote organ injury induced through lower extremity I/R. NAC is reported to be targeting oxidized lipids [21]. Tissue MDA levels were significantly reduced in NAC pretreated rats meaning a reduced lipid peroxidation and ferroptosis. NAC is known to be a glutathione precursor and also a free radical scavenger that it exerts a direct antioxidant action through this property [22]. An important rate-limiting precursor of cellular GSH synthesis is cysteine and NAC exerts its indirect anti-oxidant action by de-acetylation to cysteine thus enhances the glutathione-S-transferase activity and supplies GSH for glutathione peroxidase-catalyzed detoxification of peroxides. GSH depletion is suggested to lead to an iron-dependent accumulation of ROS, which can cause cell death [3]. Our results suggested that tissue levels of GSH significantly increased in the NAC pretreated rats indicating a reduction in ferroptosis. NAC also exhibits anti-inflammatory properties through inhibiting the activation of NF-κB to prevent the release of pro-inflammatory cytokines and thus lead to less ROS production [12]. We used a NAC dose of 150 mg/kg body weight through the intraperitoneal route. The NAC dose was lower than those used in the literature, who reported that higher doses (300 mg/kg body weight) of NAC before ischemia improved liver and lung functions more efficiently than did lower doses (150 mg/kg body weight) [23,24]. We used the NAC dose that is mainly the preferred dose in the prevention of contrast-induced nephrotoxicity. We noted that administering NAC before lower limb I/R even in lower doses protected against remote organ injury in the lungs. The rats treated with NAC had significantly lower MDA levels, higher GSH levels and less neutrophil sequestration in the lungs after IR injury than the untreated rats.

Furthermore, we evaluated H&E staining and histopathological scores and lung wet-dry weight ratio. The results revealed the evidence of lung injuries such as accumulation of neutrophils, atelectasis, thickening of alveolar inter wall and alveolar edema in control group rats. Iron accumulation in the lungs was observed in Prussian Blue staining of lung tissue in control group animals revealing iron-dependent cellular damage, namely ferroptosis. However, the histopathological scores were significantly lower in NAC pretreated animals and additionally the amount of stainable iron was significantly reduced in NAC pretreated rats. NAC has been reported to be able to chelate metals, including iron [21]. Although we did not analyze the iron levels in the present study, we could able to show that the amount of stainable iron in lung tissues of control animals was significantly higher than NAC pretreated animals.

Our study has several limitations. First, we did or could not measure the tissue or blood levels of iron that has the main role in ferroptosis. Second, we did not compare the different doses of NAC; however, the NAC dose used in the present study indicated a significant protective effect when compared to the control group and this dose regimen has no restriction for the use in clinical settings.

Conclusion

Pretreatment with NAC potentially protects against injuries to remote organs, such as the lungs. NAC pretreatment improved edema, attenuated inflammation, and reduced lung injury severity in our lower extremity I/R rat model. These data are of clinical value, particularly given the common use, common dose and relative safety of NAC.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Turkish Journal of Clinics and Laboratory

To cite this article: Simsek EK, Haberal B. Effects of single high dose topical tranexamic acid administration on bleeding and complicatıons after total knee arthroplasty surgery:A retrospective clinical study? Turk J Clin Lab 2020; 4: 294-299.

Original Article

Effects of single high dose topical tranexamic acid administration on bleeding and complications after total knee arthroplasty surgery:A retrospective clinical study

Tek seferlik yüksek doz topikal traneksamik asit uygulamasının total diz artroplastisi sonrası kanama ve komplikasyonlar üzerine etkisi: Retrospektif klinik çalışma

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Abstract

Aim: There is no consensus on the optimal method of Tranexamic acid (TA) usage in orthopaedic surgery in the literature. The aim of this study is to evaluate the effects of single high dose (3g) topical TA application on postoperative bleeding and complications in total knee arthroplasty (TKA) surgery.

Material and Methods: We retrospectively evaluated patients who underwent TKA in our clinic between January 2016 and June 2018. The patients were divided into two groups according to TA administration: Group 1 (topical TA, n=105/242) and Group 2 (non-TA, n=137/242). Demographic parameters, comorbidities, high-risk factors, preoperative hemoglobin (Hb) level, lowest postoperative Hb level, change in Hb, total drainage output, presence or absence of a transfusion, amount of blood transfused, length of stay, and complications were evaluated.

Results: In group 1, postoperative first- and second-day Hb levels were significantly higher than those in group 2. The blood loss on the day of surgery, the blood loss on the first postoperative day and total drain blood loss were significantly lower in group 1. It was determined that the patients in group 2 needed significantly more blood transfusions and had more length of hospital stay. There was no statistical difference in complications between the two groups.

Conclusion: Topical TA application effectively and significantly reduces blood loss and transfusion rates after surgery, without serious side effects, in patients undergoing primary TKA. This also reduces the length of the hospital stay.

Keywords: Total knee arthroplasty; tranexamic acid; blood loss; transfusion; complication

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Recevied: 20.07.2020 accepted: 29.08.2020
Doi: 10.18663/tjcl.791064

Öz

Amaç: Literatürde ortopedik cerrahide Traneksamik asit (TA) kullanımının optimal yöntemi konusunda fikir birliği yoktur. Bu çalışmanın amacı, total diz artroplastisi (TDA) cerrahisinde tek yüksek doz (3g) topikal TA uygulamasının postoperatif kanama ve komplikasyonlar üzerine etkilerini değerlendirmektir.

Gereç ve Yöntemler: Ocak 2016 - Haziran 2018 tarihleri arasında kliniğimizde TDA uygulanan hastalar retrospektif olarak değerlendirildi. Hastalar TA uygulamasına göre iki gruba ayrıldı: Grup 1 (topikal TA, n = 105/242) ve Grup 2 (TA olmayan, n = 137/242). Demografik parametreler, komorbiditeler, yüksek risk faktörleri, preoperatif hemoglobin (Hb) düzeyi, postoperatif en düşük Hb düzeyi, Hb'deki toplam değişiklik, toplam dren çıkışı, transfüzyon varlığı veya yokluğu, transfüzyon yapılan kan miktarı, hastanede kalış süresi ve komplikasyonlar değerlendirildi.

Bulgular: Grup 1'de postoperatif birinci ve ikinci gün Hb seviyeleri grup 2'ye göre anlamlı olarak yüksekti. Grup 1'de ameliyat günü kan kaybı, ameliyat sonrası ilk gün kan kaybı ve toplam dren kan kaybı anlamlı olarak daha düşüktü. Grup 2'deki hastaların anlamlı olarak daha fazla kan transfüzyonuna ihtiyaç duydukları ve hastanede kalış sürelerinin daha uzun olduğu belirlendi. İki grup arasındaki komplikasyonlarda istatistiksel olarak anlamlı fark saptanmadı.

Sonuç: Bu çalışmada, TA'nın yara kapatıldıktan sonra diz eklemine topikal uygulaması; primer TDA yapılan hastalarda tromboembolik riskte bir artış yaratmadan, postoperatif Hb kaybını ve kan kaybını önemli ölçüde azaltmıştır. Bu durum hastanede kalış süresini de azaltmaktadır.

Anahtar kelimeler: Total diz artroplastisi; traneksamik asit; kan kaybı; transfüzyon; komplikasyon

Introduction

Osteoarthritis (OA), also known as degenerative joint disease, is a cartilage disease characterised by the progressive loss of the structure and function of articular cartilage, where the synovial joints are involved. The treatment of OA is multifaceted and includes patient education, lifestyle changes, rehabilitation, painkillers, intra-articular injections, needle lavage, and surgical treatment. Total knee arthroplasty (TKA) is the most common method in the surgical treatment of OA in orthopaedic practice.[1]

Trauma during TKA surgery triggers the coagulation cascade and local fibrinolysis. The deflating of the tourniquet, which is used to prevent bleeding during surgery, increases the fibrinolysis and increases the bleeding. Thus, bleeding can increase after surgery, and 10-38% of patients require a blood transfusion. The average blood loss per patient can be 1,450-2,000 ml.[2]

Anaemia causes hypovolemic shock, renal failure, cardiac problems, and wound healing problems. Complications, such as allergic reactions, bacterial/viral infections, transfusion-related acute lung injury, blood type incompatibility, hemolysis, and impaired metabolic balance due to blood transfusion for the treatment of acute anaemia, significantly increase mortality and morbidity. Medical expenses also increase as a result of blood transfusion and prolonged hospital stay, which is caused by these morbidities. For this reason, in the literature, the number of studies has been increasing recently to find ways to minimise blood loss and the need for blood transfusion.[3]

Tranexamic acid (TA), a synthetic anti-fibrinolytic agent, prevents fibrinolysis by blocking plasmin formation from plasminogen. The clot becomes stabilised due to reduced numbers of fibrin monomers and decreasing fibrinogen degradation.[4] Although TA has been used in cardiothoracic surgery, gynecologic bleeding and acute trauma for more than 40 years, its use in orthopaedic surgery has become widespread only in recent years. TA has intravenous, oral, and topical administration routes.[5] In the literature, it is reported that TA, which is applied after TKA, decreases the bleeding significantly without increasing the thromboembolic risk. However, patients with a history of renal failure, thromboembolic disorder, previous stroke, myocardial infarction, deep vein thrombosis, or pulmonary embolism are considered to be at high risk, and intravenous administration is considered to be contraindicated. Topical TA application is an alternative in these patients.[6] Although many studies have compared the efficacy of intravenous and topical administration of TA, there is no consensus on the optimal method of administration in the literature.

The purpose of this study is to evaluate the effects of single high dose topical TA application on postoperative bleeding and identify possible complications in healthy and high-risk patients.

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Material and Methods

Topical TA has been routinely applied with TKA in our clinic since 2017. Patients who underwent TKA in our clinic between January 2016 and June 2018 were retrospectively analysed. After exclusion of revision arthroplasties, unicompartmental knee replacements, oncological cases, traumas, patients with anticoagulant allergies, and patients with previous knee surgeries and hardware removal, 242 of the 266 patients were included in the study (Table 1). Data were collected from patients' electronic medical records. Demographic parameters (age, sex, and side of the surgery), comorbidities (e.g., hypertension, diabetes mellitus, arrhythmia, and coronary artery disease), high-risk factors (chronic heart failure, venous thromboembolism, stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism), preoperative hemoglobin (Hb) level, lowest postoperative Hb level, change in Hb, total drainage output, presence or absence of a transfusion, amount of blood transfused, length of stay, and complications (e.g., wound healing problems, effusion, and infections) were evaluated. This study was approved by our Institutional Review Board (Project no.KA18/355). Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

The patients were divided into two groups according to TA administration: Group 1 (topical TA, n=105/242) and Group 2 (non-TA,n=137/242).Both groups were compared statistically.

All patients received TKA surgery after standard pre-operative preparation and under regional spinal/epidural anaesthesia. A prophylactic antibiotic regime was given perioperatively with intravenous injection of cefazoline sodium (1 gr) (Cezol; Deva Holding AŞ, İstanbul, Turkey) 30 minutes before tourniquet inflation and every 8 hours afterward until the suction drain was removed. During surgery, patients were in a supine position with a tourniquet on the thigh. All the surgeries were performed by the medial parapatellar approach using two different cemented knee prostheses:(1) Scorpio+ single-axis system posterior stabilized, Stryker Howmedica Osteonics, Allendale, NJ, and (2) Sigma Primary Knee System posterior stabilized, DePuy Synthes Inc., Warsaw, IN. After all components were cemented in place,the tourniquet was deflated. Following bleeding control, the joint was irrigated with normal saline and suctioned out. Intra-articular suction drains were routinely applied. Then the wound was closed, and, for group 1 (topical TA), 3g of TA was applied via the suction drain without any dilution with saline. The negative suction drain was clamped for 30 minutes to obtain the full effect of topical TA application and then opened in group 1. The same procedure was applied to Group 2 without TA administration. Total drain output, haemoglobin, and hematocrit levels were recorded daily postoperatively. The criteria for blood transfusion were a haemoglobin concentration of <8 g/dl or a haemoglobin level of <10 g/dl if the patient had any signs of anaemia (e.g., unexplained tachycardia or hypotension unresponsive to fluid replacement). For every 1g/dl of haemoglobin drip, one unit of packed red cells (330 ml) was transfused. Enoxaparin sodium (40mg) (Oksapar; Koçak Farma İlaç ve Kimya Sanayi, İstanbul, Turkey) and deep vein thrombosis stockings were used during the hospital stay for coagulation prophylaxis. After discharge, coagulation prophylaxis was provided with oral rivaroxaban (10 mg) (Xarelto; Bayer AG, Leverkusen, Germany) therapy for 21 days. Isometric exercises, passive, and active mobilization exercises with full weight-bearing were started immediately after surgery. Sutures were removed at 2 weeks postoperatively. Patients were examined daily during hospitalization and examined every 15 days after discharge for any complications.

The data were analyzed using SPSS Statistics for Windows Version 25.0 (released in 2017, IBM Corp., Armonk, NY). Continuous variables were represented by numbers and percentages; continuous variables were presented with their mean and SD values. To compare categorical and continuous variables between groups,the Chi-square test and independent samples t-test were used,respectively. The statistical significance was set at $p<0,05$.

Results

Demographics

A total of 242 patient results were evaluated. Table 1 shows the demographic characteristics of the patients. There were no statistically significant differences in demographics.

Hemoglobin levels and blood loss

The preoperative Hb levels of the patients was 13,04 ± 1,15 mg/dl (mean ± SD) in group 1 and 13,23 ± 1,42 mg/dl in group 2. Hemoglobin levels were recorded postoperatively on the day of surgery and for the following 3 days. In group 1, postoperative first- and second-day Hb levels were significantly higher than those in group 2 ($p<0,001$). The difference between the highest and lowest Hb values obtained after surgery was termed as the maximum Hb decrease and it was significantly higher in group

2 (3,33 ± 0,90 mg/dl) than group 1(3,89 ± 1,19 mg/dl) (p<0,001). When the records of the amount of blood loss through the drain were examined, it was determined that both the blood loss on the day of surgery (p<0,001), the blood loss on the first postoperative day (p=0,033) and total drain blood loss (p<0,001) were significantly lower in group 1(Table 2).

Table 1: Demographic Characteristics of the Study Population

Variables*	Group 1 [N(%)]	Group 2 [N(%)]
Sex		
• Female	94 (%89.5)	110 (%80.3)
• Male	11 (%10.5)	27(%19.7)
Co-Morbidities		
• Arrhythmia	16 (%15.2)	13 (%9.5)
• DM	24 (%22.9)	48 (%35)
• HT	81 (%77.1)	105 (%76.6)
• CHD	19 (%18.1)	17 (%12.4)
High Risk Factors		
• CRF	4 (%3.8)	2 (%1.5)
• DVT	0 (%0.0)	2 (%1.5)
• MI	2 (%1.9)	3 (%2.2)
Side		
• Right	58 (%55.2)	75 (%54.7)
• Left	47 (%44.8)	59 (%43.1)
• Bilateral	0 (%0.0)	3 (%2.2)
Complications		
• WHP	2 (%1.9)	3 (%2.2)
• Effusion	3 (%2.9)	6 (%4.4)
• Pneumonia	1 (%1.0)	2 (%1.5)
• Amputation	0 (%0.0)	1 (%0.7)

*DM=Diabetes Mellitus, HT=Hypertension, CHD=Coronary Heart Disease, CRF=Chronic Renal Failure, DVT=Deep Vein Thrombosis, MI=Myocardial Infarction, WHP=Wound Healing Problems

Blood Transfusion

A total of 46 units of erythrocyte suspension (ES) were given to 30 of 105 patients (28,5%) in group 1, and 82 of 137 patients (59,8%) in group 2 received 186 units of ES (Table3).When the number of blood transfusions was evaluated statistically, it was determined that the patients in group 2 needed significantly more blood transfusions (p<0,001). When the average cost of the ES to the social security system was calculated, it was determined that the application of tranexamic acid lowered the cost of blood products for the patients included in this study by approximately 5,600 USD (Table 3).

Hospital Stay

Patients in group 1 had a mean hospital stay of 4,94 days compared with 5,27 days for patients in group 2, and there were statistically significant differences between the two groups (p=0,034) (Table 2).

Table 2: Comparison of Outcomes

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P* Value
Age	72,21 ± 7,41	69,96 ± 7,63	0.022
Pre-op. Hemoglobin (mg/dl)	13,04 ± 1,15	13,23 ± 1,42	0.269
Postop. Hemoglobin 0 (mg/dl)	11,5 ± 1,34	11,45 ± 1,41	0.785
Postop. Hemoglobin 1 (mg/dl)	10,84 ± 1,23	10,24 ± 1,07	<0.001
Postop. Hemoglobin 2 (mg/dl)	10,41 ± 1,11	9,97 ± 1,01	<0.001
Postop. Hemoglobin 3 (mg/dl)	10,31 ± 0,93	10,11 ± 0,87	0.088
Postop. Hemoglobin 4 (mg/dl)	10,36 ± 0,86	10,42 ± 1,01	0.678
Max. Hemoglobin decrease (mg/dl)	3,33 ± 0,90	3,89 ± 1,19	<0.001
Postop. 0 Drain Blood Loss (ml)	245,19 ± 149,42	786,53 ± 444,56	<0.001
Postop. 1 Drain Blood Loss (ml)	178,16 ± 84,53	212,57 ± 159,74	0.033
Total Drain Blood Loss (ml)	423,35 ± 193,92	997,91 ± 516,45	<0.001
Transfusion (number)	0,44 ± 0,74	1,36 ± 1,58	<0.001
Length of Stay (Day)	4,94 ± 0,86	5,27 ± 1,51	0.034

*p<0.05 was statistically different

Table 3: Transfusion Data and approximate costs

	TNP	NPUBT	NES (Unit)	Approximate Costs (USD)
Group 1 (TXA+)	105	30	46	1800
Group 2 (TXA-)	137	82	186	7500
Total	242	112	232	9300

TNP: Total Number of patients, NPUT: Number of patients undergoing blood transfusion, NES: Number of ES

Complications

There were 6 complications in group 1 (2 wound healing problems, 3 cases of articular effusion, and 1 case of pneumonia) and 12 in group 2 (3 wound healing problems, 6 cases of articular effusion, 2 cases of pneumonia, and 1 acute arterial thrombosis of the lower extremity resulting in amputation) (Table 1). No coagulation-related complications were found in any patient included in the study. There was no statistical difference in complications between the two groups.

Discussion

In our clinic, as indicated in the literature, a topical administration is preferred to minimize systemic absorption

of TA and thus prevent thromboembolic side effects.[6,7] In previous studies, both low-dose (500 mg) and high-dose (3 g) TA administration has been shown to be effective in reducing blood loss after surgery.[8,9] Recent studies have shown that high-dose topical TA administration is more effective.[4,10] For this reason, we preferred high-dose TA application in our clinical practice.

In this study, topical administration of TA via suction drain to the knee joint after wound closure significantly reduced post-operative Hb loss and blood loss in patients having a primary TKA. In the topical TA group, Hb values were significantly higher than in the non-TA group on the first and second post-operative days, which is consistent with reports in the literature [11,12]. However, no significant difference was found between the post-operative Hb values obtained on the day of surgery. Hemodilution due to intravenous fluid and drug administration, which is applied more intensively during and soon after surgery, may cause this result. Similar to the results obtained in previous studies, the blood loss through the drain on the day of surgery and the first post-operative day and the total drain blood loss in the topical TA group were significantly lower than in the non-TA group.[4,13] After primary TKA surgery, bolus blood loss occurs due to tourniquet use.[14] In the topical TA group, both TA administration and closure of the suction drain for 30 minutes after application may prevent bolus blood loss and result in decreased total drain output.

Previous studies have shown that intravenous TA protocols, both during and after surgery [11, 14, 15] and topical TA applications, including periarticular injections.[5, 9, 16] reduce blood transfusion rates compared with a placebo after primary TKA surgery. However, in the studies, different topical doses of TA (1g, 1,5g, 2g, and 3g) were not superior to each other.[4, 9, 10] In this study, 3g of TA was applied topically and there was a statistically significant decrease in blood transfusion rates compared with the non-TA group, which isconsistent with reports in the literature.

TA application reduces blood loss after surgery and affects the recovery period both locally and systemically. Decreased intra-articular hemorrhage reduces hematoma formation and joint swelling, and thus fewer wound healing problems occur. This increases compliance with isometric exercises and passive and active mobilization exercises, and generally accelerates mobilization. Consequently, local complications that prevent mobilization, such as joint contracture, are avoided. When systemic effects are evaluated, decreasing blood loss reduces the incidence of postoperative anemia and thus prevents anemia-related symptoms that reduce early mobilization, such as dizziness, shortness of breath, and fatigue. As a result of these effects, as shown in our study, the duration of hospital stay was significantly reduced in patients treated with TA.

Previous studies in the literature have shown that topical TA can be used safely even in patients with high thromboembolic risk. Abdel et al. compared the effects of topical and intravenous TAadministration after primary TKA and found thromboembolic disorder in 2 of 320 patient (0,6 %).[13] Wong et al. examined the effect of topical TA application on blood loss after surgery and reported thromboembolic disorder in 3 of 31 patients treated with 1,5g of TA and 1 of 33 patients treated with 3g of TA. They observed thromboembolic disorder in 2 of 35 placebo patients and reported that there was no statistically significant difference between the groups. [9] We encountered thromboembolic disorder in only 1 of the 242 patients included in our study, and this patient was in group 2 (non-TA group). In addition, we did not find any statistically significant difference between the groups when all the complications were evaluated.

The present study had several limitations. First, our study is a retrospective study and no power analysis was performed to determine the size of the study population. Second, in our clinic, we only administer a single high dose (3g) of topical TA after primary TKA. Therefore, we could not compare the results to other reported results using different administration procedures. Third, our data reflect short-term results and therefore we could not evaluate the effects of TA application in the long-term follow-up period.

Conclusions

In conclusion,our clinical practice and results support that topical TA application effectively and significantly reduces blood loss and transfusion rates after surgery,without serious side effects, in patients undergoing primary TKA. This reduces the length of the hospital stay.In addition, further studies are needed to determine the optimal dose range and route of administration of TA and thus establish “gold standard” treatment protocols.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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Turkish Journal of Clinics and Laboratory

To cite this article: Turan DB. Yara kültürleri sonuçlarının Q skorlaması ile birlikte analizi 2020; 4: 300-306.

Orijinal Makale

Yara kültürleri sonuçlarının Q skorlaması ile birlikte analizi

Analysis of wound cultures results with Q scoring

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Öz

Amaç: Yara kültürleri sonuçlarının yara örneği kalitesi ile birlikte değerlendirilmesi klinisyene etkenin saptanması konusunda önemli bilgi sağlamaktadır. Yara örneğinin kalitesi Q skorlaması ile yapılabilmektedir. Üçüncü basamak hastanemizde takip edilen hastalara ait yara örneklerinin kültür sonuçlarının, örneklerin mikroskobik incelemesiyle saptanan Q skorlaması kullanılarak analiz edilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya yara enfeksiyonu ön tanısıyla başvuran ya da yatarak takip edilen toplam 311 hastadan alınan yara kültürü örneği dahil edildi. Yara kültüründe üreyen mikroorganizmalar tam otomatize VITEK II Compact (Biomeriux, Fransa) sistemle identifiye edildi. Ayrıca örneklerin düşük büyütme X10 ile yapılan mikroskobik incelemesinde her alanda görülen polimorfnüveli lökosit (nötrofil) ve epitel hücre sayıları kaydedildi ve bu sayılara göre her bir örnek için Q skorları belirlendi. Gruplar arasındaki farklılıklar ki kare testi ile analiz edildi.

Bulgular: Yara kültürlerinin 226'sı (%72.7) Q1 veya üzeri Q skoruna sahipti. Üreme görülmeyen kültürlerin %20'si, üreme olanların ise %80'i Q2 veya üzeri Q skoruna sahipti. Bir veya daha fazla patojen etkenin görüldüğü örneklerin %85.2'si Q1 veya üzeri Q skoruna sahipken, cilt florası bakterilerinin %71.3'ü Q1 veya üzeri Q skoruna sahipti, bu oranlar arasındaki fark istatistiksel olarak anlamlı idi (p=0.0154). Cilt florası dışındaki patojen etkenler içinde en sık üreyen mikroorganizmalar metisiline duyarlı *Staphylococcus aureus* (%21.7), metisiline dirençli *S.aureus* (%13.3) idi.

Sonuç: Çalışmamızda özellikle Q0 skorlu örneklerin reddedilmesi gerektiği, bu örneklerin çalışılması halinde maliyete ve hasta için zaman kaybına yol açabileceği ve klinisyeni tanı ve tedavi açısından yanlış yönlendirebileceği görülmüştür. Verilerimizin araştırmacılara ve klinisyenlere katkı sağlayacağı, yara kültürlerinin işlenme ve değerlendirmesi bakımından bir kılavuz oluşturulması gerektiği düşüncesindeyiz.

Anahtar kelimeler: Yara yeri enfeksiyonu; yara kültürü; Q skoru

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Doi: 10.18663/tjcl.637673

Abstract

Aim: The evaluation of the results of the wound cultures together with the quality of the wound samples provides important information on the determination of the agent to the clinician. The quality of the wound sample can be done using Q scoring. In our study, we aimed to analyze the culture results of the wound samples of patients who were followed in our tertiary care hospital using the Q score determined by microscopic examination of the samples.

Material and Methods: Wound culture specimens taken from a total of 311 patients who were admitted to with a preliminary diagnosis of wound infection were included in the study. Microorganisms growth in the wound cultures were identified. In addition, numbers of polymorphonuclear leukocytes (neutrophil) and epithelial cells in each are a observed by microscopic examination of the samples with low magnification, and Q scores were determined for each sample according to these numbers. Differences between the groups were analyzed using Pearson's Chi Square Test.

Results: Of the wound cultures, 226 (72.7%) had Q1 or higher Q scores. 20% of the cultures with no growth and 80% of the cultures with growth had Q2 or higher Q scores. 85.2% of the samples with one or more pathogenic agents had Q1 or higher Q scores, 71.3% of skin flora bacteria had Q1 or higher Q scores, the difference between these rates was statistically significant (p=0.0154). The most common pathogenic microorganisms other than skin flora were the methicillin-susceptible *S. aureus* (21.7%) and methicillin-resistant *Staphylococcus aureus* (13.3%).

Conclusion: In our study, it was found that Q-score samples should be rejected, and that in case these sample sare proecessed, it will cause costand and time loss for the patient, and that may mislead the clinician in terms of diagnosis and treatment. We think that our findings will contribute to researchers and clinicians, and that a guide should be established in terms of processing and evaluation of wound cultures.

Keywords: Wound site infection; wound culture; Q score.

Giriş

Birçok faktöre bağlı olarak gelişen yaralar cilt veya doku bütünlüğünün bozulmasından dolayı dış ortama ve mikroorganizmalar tarafından kontamine edilmeye açıktırlar. Yara yerlerinde enfeksiyon gelişmesi hastayı ve klinisyeni zor durumda bırakan, ancak çok sık görülen bir durumdur. Yara yeri enfeksiyonları ciddi istenmeyen durumlara yol açabilmektedir. Bu nedenle yara yeri enfeksiyonlarının tedavilerinin belirlenmesi büyük önem taşımaktadır [1-3].

Yara enfeksiyonlarının tedavisinin belirlenmesinde mikrobiyoloji laboratuvarlarına önemli rol düşmektedir. Yara yerinde enfeksiyon olup olmadığının belirlenmesinde laboratuvar verileri yol göstericidir.Yara yerinden alınan örneklerin mikroskobik inceleme ve kültür sonuçlarının en uygun şekilde bildirilmesi kritik öneme sahiptir. Yara kültüründe üreyen mikroorganizmanın belirlenmesi tedavinin yönlendirilmesinde yol gösterici olsa da, üreyen her mikroorganizmanın potansiyel enfeksiyon etkeni olmadığı bilinmektedir [3-5]. Bu nedenle alınan örneğin kalitesinin belirlenerek üreyen mikroorganizmanın kontaminan mı yoksa olası bir enfeksiyon etkeni mi olduğunun belirlenmesinde laboratuvar verilerinin rolü büyüktür [6-8]. Örneğin kalitesinin saptanması için mikroskobik inceleme ile belirlenen polimorf nüveli lökosit ve epitel hücresi sayılarının ilişkisiyle hesaplanan Q skoru fayda sağlamaktadır. Q skoruna göre üreyen mikroorganizmaların kontaminan flora bakterileri mi potansiyel enfeksiyon etkeni mi olduğu daha net belirlenebilmektedir [8].

Yara enfeksiyon etkenlerinin dağılımı hem yaranın vücuttaki lokalizasyonuna hem de sağlık merkezinin yerine göre değişebilmektedir. Bu nedenle yara enfeksiyonu etkenlerinin farklı merkezlerden bildirilmesi gerekliliği bulunmaktadır [6,7]. Çalışmamızda üçüncü basamak hastanemizde takip edilen ve çeşitli nedenlerden dolayı yara gelişen hastalara ait yara örneklerinin kültür sonuçlarının, örneklerin mikroskobik incelemesiyle saptanan Q skorlaması kullanılarak analiz edilmesi amaçlanmıştır.

Gereç ve Yöntemler

Örnekler ve Testler

Çalışmaya üçüncü basamak hastanemize yara enfeksiyonu ön tanısıyla başvuran ya da yatarak takip edilen toplam 311 hastadan alınan yara kültürü örneği dahil edildi. Yara

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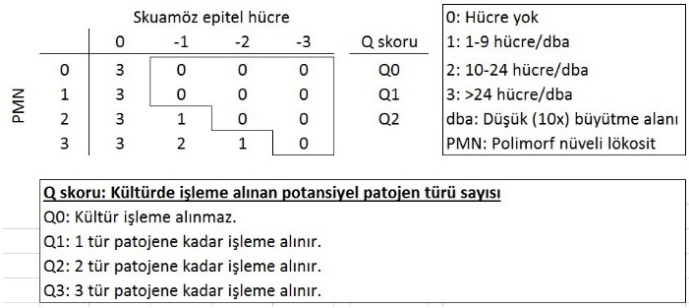
yerlerinden steril eküvyon çubuğu ile uygun şekilde alınan sürüntü örnekleri Stuart taşıma besiyeri ile mikrobiyoloji laboratuvarına transfer edildi. Sürüntü örnekleri %5 koyun kanlı agar, çikolatamsı agar ve eozin metilen mavisi (EMB) agar besiyerlerine ekildi ve 35° C'de aerop koşullarda 24-48 saat inkübe edildi. İnkübasyon sonunda üreme görülen besiyerlerindeki koloniler otomatize identifikasyon sistemi ile (Vitek® II Compact, BioMerieux, Fransa) identifiye edildi.

Sürüntü örneklerinden ayrıca Gram (Gül Biyoloji, Türkiye) boyama preparatları hazırlandı. Gram boyamanın mikroskobik incelemesinde X100 büyütmede görülen mikrobiyolojik yapılar kaydedildi.

Q skorlama sistemi her 10x'lik düşük büyütme alanında görülen epitel hücre sayısı eksi puan olarak, nötrofil sayısı artı puan olarak eklenerek sayısal bir değer olarak 'Q skoru' oluşturulması prensibine dayanır. Algoritma şekil 1'de gösterilmiştir. Yara kültür örneklerinin Gram boyalı mikroskobik incelemesinde görülen polimorf nüveli lökosit (nötrofil) ve epitel hücre sayıları kaydedilerek, bu sayılara göre her bir örnek için Q skoru hesaplandı.



Şekil 1: Q skoru hesaplanmasında uygulanan algoritma (Matkovski ve ark.'nın [8] çalışmasından adapte edilerek düzenlenmiştir).

Bu çalışma 10.02.2020 tarihli 2020/02 sayılı etik kurul onayı alındı. Çalışma retrospektif olarak planlanmıştır. Helsinki Deklarasyonu ilkelerine uyuldu ve hastalardan onam belgeleri alındı.

İstatistiksel analiz

Çalışmadaki tüm istatistiksel analizler SPSS 25.0 yazılımı (IBM SPSS, Chicago, IL, USA) kullanılarak yapıldı. Tanımlayıcı veriler sayı ve yüzde olarak verildi. Kategorik değişkenler açısından gruplar arasındaki karşılaştırmalar Ki Kare testi ile yapıldı. Sonuçlar %95 güven aralığında değerlendirildi ve $p<0.05$ değerleri anlamlı kabul edildi. Gerekli yerlerde Bonferoni düzeltmesi yapıldı.

Bulgular

Hastaların 192'si (%61.7) erkek, 119'u (%38.3) kadındı. Hastaların yaş ortalaması 47.5±19.1 yıl (Yaş aralığı 1-74 yıl) idi. Örneklerin en sık gönderildiği klinikler dermatoloji (66 örnek, %21.2) ve el cerrahisi ve mikrocerrahi (56 örnek, %18) idi. Hastaların 30'unda anamnezde (%9.6) diabetes mellitus mevcuttu.

Yara kültürlerinin 226'sı (%72.7) Q1 veya üzeri Q skoruna sahipti. Üreme görülmeyen kültürlerin %23,9'u, üreme olanların ise %76,1'i Q1 veya üzeri Q skoruna sahipti (Tablo 1).

Üreme görülen kültürlerden, cilt florası üreyenlerde Q skoru Q0 olanların oranı (%28.8) 1 veya daha fazla patojen üreyenlerdeki Q0 skoru olanların oranına (%15.5) göre anlamlı yüksek bulundu (p=0.043).

Bir veya daha fazla patojen etkenin görüldüğü örneklerin %85.2'si Q1 veya üzeri Q skoruna ve cilt florası bakterilerinin %71.2'si Q1 veya üzeri Q skoruna sahipti, bu oranlar arasındaki fark istatistiksel olarak anlamlı idi (p=0.0154). Ayrıca bir veya daha fazla patojen etkenin görüldüğü örneklerin %65.3'ünün Q skoru Q2 idi, cilt florası bakterilerinin ise %49.3'ünün Q skoru Q2 idi, bu oranlar arasındaki fark da istatistiksel olarak anlamlı idi (p=0.0324) (Tablo 1).

Tablo 1: Üreme sonuçlarının Q skorlarına göre dağılımı [n(%)].

Kültür sonucu	Q0	Q1	≥Q2	≥Q1
Üreme yok (n=96)	42	22	32	
Üreme var (n=215)	43	44	128	
Cilt florası bakterileri (n=73)	21 (28.8)	16 (21.9)	36 (49.3)	52 (71.2)
≥1 Patojen etken (n=142)	22 (15.5)	28 (19.9)	92 (65.3)	120 (85.2)
p*	0.043		0.0324**	0.0154***
Toplam	85	66	160	

*p değerleri cilt florası bakterileri ile ≥1 Patojen etken değişkenleri arasındaki analizleri göstermektedir. **p değeri Q skoru Q2 ve üzeri olanlar ile Q2'den düşük olanlar arasında hesaplanmıştır. ***p değeri Q skoru Q1 ve üzeri olanlar ile Q0 olanlar arasında hesaplanmıştır.

Cilt florası dışındaki potansiyel patojen etkenler içinde en sık üreyen mikroorganizmalar metisiline duyarlı *Staphylococcus aureus* (MSSA) (26 örnek, %21.7), metisiline dirençli *Staphylococcus aureus* (MRSA) (16 örnek, %13.3) ve *Pseudomonas aeruginosa* (10 örnek, %8.3) idi (Tablo 2).

Klinik tanı dağılımına göre toplam 120 örnek (%38.6) komplike olmayan deri ve yumuşak doku enfeksiyonu (DYDE), 62 örnek (%19.9) travmatik yara enfeksiyonu, 47 örnek (%15.1) komplike deri ve yumuşak doku enfeksiyonu idi (Tablo 3).

Tablo 2: Cilt florası dışındaki etken mikroorganizmalarının Q skorlarına göre dağılımı [n(%)].

Mikroorganizmalar	Q skoru				Toplam
	Q0	Q1	≥Q2	≥Q1	
MSSA	2	5	19	24	26
MRSA	3	3	10	13	16
Pseudomonas aeruginosa	1	2	7	9	10
Escherichia coli	1	2	5	7	8
Enterococcusfaecalis	3	1	2	3	6
Acinetobact er baumannii	0	4	1	5	5
Enterobacter cloaca	0	0	5	5	5
E. coli + *Proteus mirabilis*	0	0	5	5	5
Klebsiella pneuomoniae	0	0	4	4	4
A grubu beta hemolitik streptokok	0	0	3	3	3
Diğer	11	11	31	42	32
Toplam	21	28	92	120	120

MSSA: Metisiline duyarlı *Staphylococcus aureus*, MRSA: Metisiline dirençli *Staphylococcus aureus*.

Tablo 3: Q skorlarına göre tanı dağılımı [n(%)].

Tanı	Q skoru				Toplam
	Q0	Q1	≥Q2	≥Q1	
Komplike olmayan DYDE	35 (29.2)	25 (20.9)	60 (50)	85 (70.9)	120
Travmatik yara	22 (35.5)	15 (24.2)	25 (40.4)	40 (64.6)	62
Komplike DYDE	4 (8.6)	6 (12.8)	37 (78.8)	43 (91.5)	47
Diyabetik yara	2 (7.7)	11 (42.4)	13 (50)	24 (92.4)	26
Yüzeyel CAE	9 (69.3)	1 (7.7)	3 (23.1)	4 (30.8)	13
Diğer	13 (30.3)	8 (18.7)	22 (51.2)	30 (69.8)	43
Toplam	85 (27.4)	66 (21.3)	160 (51.5)	226 (72.7)	311

DYDE: Deri ve yumuşak doku enfeksiyonu, CAE: Cerrahi alan enfeksiyonu.

Tartışma

Yara yerinin mikroorganizmalar tarafından enfekte edilmesi çok sık ve istenmeyen bir durumdur. Yara yerinde gelişen enfeksiyon, yaranın iyileştirmesini geciktirir ve ciddi komplikasyonlara neden olabilir. Bu nedenle yara enfeksiyonlarının doğru ve hızlı tedavisi hasta açısından kritik öneme sahiptir. Yara enfeksiyonunun uygun tedavisinin belirlenebilmesi için enfeksiyon etkeninin doğru saptanması gereklidir. Yara enfeksiyonlarına etken ajanların zamana ve bölgeye, hatta sağlık merkezine göre değişkenlik gösterebilmesi enfeksiyon etkeninin belirlenmesini daha önemli kılmaktadır. Bu nedenle her merkezin yara dahil birçok enfeksiyon etkenlerinin genel profilini belirlemesi yara enfeksiyonlarının yönetiminde bilgi sağlayıcı olmaktadır [4,7]. Çalışmada hastanemizde işleme alınan yara kültürü sonuçlarının mikroorganizma dağılımı irdelenmiştir.

Cilt normal/lokal flora açısından zengindir. Cilt florası yara yerinde enfeksiyona yol açabilmektedir. Ancak yara yerinde potansiyel enfeksiyon etkeni olarak normal flora dışındaki mikroorganizmaların belirlenmesi nispeten daha kolay olsa da cilt florasının etken olup olmadığının belirlenmesinde bazı zorluklarla karşılaşılmaktadır. Yara yerinden uygun örneğin alınmasındaki güçlükler ve örnek alınırken yapılan hatalar enfeksiyon etkeninin belirlenmesinde karışıklığa yol açabilmektedir. Bu nedenle alınan örneğin uygunluk derecesinin belirlenmesi gerekmektedir [3-5,8]. Bu bağlamda Q skorlaması geliştirilmiştir. Alınan örneğin mikroskobik incelemesindeki nötrofil ve epitel hücre sayılarının hesaplanması ile belirlenen Q skoru, kültürde üreyen mikroorganizmanın enfeksiyon etkeni olup olmadığının belirlenmesinde klinisyene yol gösterici olmaktadır [8]. Çalışmada literatürde az sayıdaki çalışmada uygulanmış olan Q skorlama sisteminden faydalanılarak yara enfeksiyonu etkenlerinin dağılımı belirlenmiştir.

Gram boyama bulunduğu tarihten günümüze kadar bakterilerin tespitinde halen önemini korumaktadır. Kolay, pratik ve ucuz bir yöntemdir. Her ne kadar mikroorganizmaların taksonomisi için özellikle kullanılmışsa da günümüzde bakteriyel vaginoz tanısında Nugent skorlaması, balgam

örneklerinin kalitesinin belirlenmesinde Bartlett skorlaması ve yara örneklerinin değerlendirilmesinde Q skorlaması ile tanısal değerini arttırmaktadır [8-10].

Q skorlaması sistemine göre yara kültürünün çalışmaya alınıp alınmayacağı, identifiye edilecek ve antibiyogram çalışılacak potansiyel enfeksiyon etkeni ve etken sayısı tespit edilebilir. Q skorlama sistemine göre Q skoru 0 olan örneklerin kültürünün çalışılmasına gerek yoktur. Q3 skoruna sahip örnekler en kaliteli örneklerdir. Skora göre tanımlanacak ve rapor edilecek potansiyel patojen sayısı Q1 için 1, Q2 için 2, Q3 için 3 olarak önerilmektedir [8,11]. Ülkemizde bu konuda yerleşik bir öğreti, kabul edilmiş bir kılavuz olmadığı için çoğu laboratuvar Q skorlama yöntemini kullanmamaktadır. Hastanemizde Q skorlama sistemini kullanmamıza rağmen bu sebeplerle Q skoru 0 olan örnekler çalışmaya alınmış, örnek reddi yapılamamıştır. Potansiyel enfeksiyon etkenleri de tiplendirilmiş ve antibiyotik duyarlılık testleri çalışılmıştır. Q skoru 0 örneklerinin kültüründe üreyen mikroorganizmanın cilt florası olma olasılığı oldukça yüksektir. Bu örneklerin reddedilmeyerek laboratuvarda çalışılması hem zaman ve iş gücü kaybına yol açar, hem de laboratuvar maliyetini arttırır. Aynı zamanda bu grup örneklerin çalışılması halinde çıkan kültür sonucunun klinisyene bildirilmesinin de sakıncası bulunmaktadır. Bu kültürlerde üreyen mikroorganizmanın kesin enfeksiyon etkeni gibi algılanma durumu, klinisyenin hastaya gereksiz yere antibiyotik tedavisi başlamasına neden olabilir. Gereksiz antibiyotik kullanımının hasta sağlığına verebileceği zararın yanı sıra yara iyileşmesi açısından bir zaman kaybı ve maliyete de yol açacağı ortadadır. Q skoru 0 olan örneklerin bu nedenlerle kültürlerinin yapılmaması gerekmektedir [2,4,8]. Çalışma verilerine göre Q0 grubu kültürlerde cilt florası üyelerinin anlamlı olarak yüksek oranda üreme varlığı bu durumu desteklemektedir. (p=0.0154 ve p=0.0324).

Çalışmada cilt florası bakterileri ve potansiyel patojen etken olarak düşünülen bakteri grubu arasında Q skorlamasına göre analiz yapılmıştır. Buna göre Q skoru Q0 olan örneklerin %49.4'ünde üreme olmazken, üreme olanların %24.7'sinde cilt florası bakterileri üremiştir. Q1 ve üzeri örneklerin %23.9'unda üreme yokken, %23'ünde cilt flora bakterileri %53.1'inde en az bir potansiyel enfeksiyon etkeni üreme olmuştur. Q1 ve üzeri örnekler karşılaştırıldığında cilt florası üremesi olan kültürlerdeki Q1 ve üzeri skorlu olanların oranı 1 ve üzeri patojen üreyenlerdeki Q1 ve üzeri olanların oranına göre anlamlı düşük bulunmuştur (p=0.0154). Bu durum Q skorlamasının gerekli olduğunu ve Q0 skorlu örneklerin dışlanması gerektiğini desteklemektedir.

Q0 olan örneklerde cilt florasına ait mikroorganizmaların üremesinde anlamlı yüksek oran olduğu görülmüştür (%28.8 vs. %15.5). Ayrıca Q skorunun hem Q1 ve üzeri olarak hem de Q1 ve Q2 olarak alındığı durumların her ikisinde de cilt florası üyelerinin anlamlı olarak daha düşük oranda ürediği belirlenmiştir. Bu veriler Q skorlamasının üreyen mikroorganizmanın etken mi kontaminan mı olduğu yönünde fayda sağlayabileceğini daha iyi göstermektedir. Ayrıca Q skorlamasında hem Q1 ve üzeri (Q1 veya Q2) hem de sadece Q1 skorunun eşik değer olarak düşünülmesinin kontaminan ayrımında yol gösterici olabileceği hakkında fikir vermektedir. Bu veriler Q0 skorlu örneklerin çalışılmaması gerektiği düşüncesini desteklemekte ve örneklerin çalışılması için en az Q1 skorunun aranması gerektiğini göstermektedir.

Çalışmada literatürdeki diğer çalışmalardan farklı olarak, yara enfeksiyonlarındaki klinik tanılarında Q skorlamasına göre dağılımı irdelenmiştir. Buna göre komplike deri ve yumuşak doku enfeksiyonu olgularının çok yüksek oranının (%78.8) Q1 ve Q2 olduğu görülmüştür. Bunun dışında komplike olmayan DYDE, travmatik yara ve diyabetik yara enfeksiyonlu olgularının çoğunun (%64-93 arası oranlarda) Q1 veya üzeri Q skoruna sahip olduğu gözlenmiştir. Oysa yüzeyel cerrahi yara enfeksiyonu tanısı ile alınan yara kültürlerindeki düşük Q skoru (Q0) oranının %70 civarında olduğu belirlenmiştir. Bu veriler beklenen bir durum olarak, yüzeyel yaralarda örnek kalitesinin daha komplike ve belirgin yaralara göre daha az uygun örnek alınabildiğini göstermektedir.

Gündem ve ark. [6] yara yeri enfeksiyon etkenlerini belirledikleri çalışmalarında en sık patojen etkenin %32.4 oranla, Sesli-Çetin ve ark. [12] ise %29.1 oranla *S. aureus*'u belirlemişlerdir. Yara enfeksiyonlarında en sık etkenin *S. aureus* olduğunu Demir ve Erandaç [13] %19'luk bir oranla, Zafer ve ark. [14]. %41.2'lik, Zer ve ark. [8] %31.2'lik, Güriz ve ark. [16] ise %28.2'lik bir oranla belirlemişlerdir. Turhanoğlu ve ark. [7]. Karadağ ve ark. [17] ve Yurtsever ve ark. [18] en sık etkeni *Escherichia coli* olarak saptamışlardır. Çalışmada en sık etken olan *S. aureus* izolatlarının patojen etkenler içinde oranı %35 (42/120) olarak ve bazı çalışmalarda en sık etken olarak belirlenen *E. coli* oranı ise patojen etkenler içinde %6.7 olarak belirlenmiştir. Çalışmalarda en sık etkenlerin *S. aureus* ve *E. coli* olarak bildirilmiş olduğu görülmekle birlikte yara yerinin lokalizasyonuna göre en sık etken ve oranları değişebilmektedir. Kolon operasyonları gibi özellikle barsak içeriği ile kontamine olma olasılığı yüksek olan lokalizasyonlarda en sık etkenin *E. coli* olması beklenen bir durumdur [19,20]. Bu olguların dışında çalışmamızdaki gibi en sık etkenin *S. aureus* olarak belirtildiği görülmektedir. Bunun dışında çalışmalar

arası bildirilen oranlarda farklılıklar görülmesinde bir neden de, bazı araştırmacıların tüm etkenler içindeki oranı bildirmesi, bazı araştırmacıların ise sadece patojen etkenler içindeki oranı vermesidir. Çalışmamızda sadece patojen etkenler içindeki oranlar belirtilerek cilt florası oranları ekarte edilmiştir.

Yara kültürlerinde cilt florasına ait mikroorganizmaların üremesi sık rastlanılan bir durumdur [3,4]. Çalışmamızda üreme görülen örneklerin %34.0'ında (73/215) cilt florası bakterileri üremiştir. Cilt florası elemanları içinde en sık üreyen %22.8'lik bir oranla (49/215) koagülaz negatif stafilokoklar (KNS) olmuştur. Yara kültürleri içinde KNS saptanma oranını Cirit ve ark. [20] %20.9, Sesli-Çetin ve ark. [12] %24, Gündem ve ark. [6] %25.3, Zer ve ark. [15] %18.4, Turhanoğlu ve ark. [7]. ise %58.5 olarak bildirmişlerdir. Bu verilerde görüldüğü üzere yara yerinde yüksek oranlarda KNS saptanmaktadır. KNS gibi cilt florası görülen durumlarda üreyen bakterinin potansiyel enfeksiyon etkeni mi yoksa lokal floraya ait kontaminan bakteri mi olduğunun ayırt edilmesi yara tedavisinin yönetimi açısından önem taşımaktadır. Bu ayrımın yapılmasında alınan örneğin kalitesinin belirlenmesi büyük fayda sağlamaktadır [3-5]. Bu gerekçeyle çoğu çalışmadakinden farklı olarak Q skorlaması kullanılmıştır. Q skorlaması sayesinde alınan örneğin kalitesine göre üremiş olan cilt florası bakterisinin etken olup olamayacağı fikri daha da netleşmektedir. Cilt florası üremesi görülen örneklerin yaklaşık %30'unun düşük Q skoruna sahip olduğu görülmüş ve bu olguların kontaminan olma olasılığının çok daha yüksek olduğu düşünülmüştür. Cilt florası üremelerinin yaklaşık yarısının yüksek Q skoruna sahip olduğu belirlenmiş ve klinisyenin uygun tedaviyi belirlemesi açısından yol gösterici olabileceği öngörülmüştür. Çalışmada cilt florası bakterileri ve patojen etken olarak düşünülen bakteri grubu arasında Q skorlamasına göre analiz yapılmıştır. Buna göre Q skoru Q1 veya üzeri olan örneklerde cilt florasına ait elemanların üremesinde anlamlı yüksek oran olduğu (%85.2 vs. %71.2) görülmüştür. Ayrıca Q skorunun hem Q1 ve üzeri olarak hem de sadece Q2 olarak alındığı durumların her ikisinde de cilt florası üyelerinin anlamlı olarak daha düşük oranda ürediği belirlenmiştir. Bu veriler Q skorlamasında hem Q1 ve üzeri (Q1 veya Q2) hem de sadece Q1 skorunun eşik değer olarak düşünülmesinin potansiyel patojen ve kontaminan mikroorganizma ayrımında yol gösterici olabileceği hakkında fikir vermektedir.

Sonuç

Hastanemizdeki yara yeri enfeksiyonu düşünülen olgulardaki kültür sonuçlarına göre üreyen mikroorganizmaların dağılımı irdelenmiştir. Literatürdeki çoğu yara kültürü odaklı çalışmadan farklı olarak alınan örneğin kalitesini ve uygunluğunu belirleyen Q skorlaması kullanılmıştır. Q skorlamasının analizlere dahil edilmesiyle üreyen mikroorganizmaların potansiyel enfeksiyon etkeni ya da kontaminan mikroorganizma olup olmadığının daha net olarak yorumlanabilmesi sağlanmıştır. Özellikle Q0 skorlu örneklerin reddedilmesi gerektiği, bu örneklerin çalışılması halinde maliyete ve hasta için zaman kaybına yol açabileceği ve klinisyeni tanı ve tedavi açısından yanlış yönlendirebileceği görülmüştür. Yara kültürlerinin sonuçlarının skorlanması klinisyene tedavi planlaması aşamasında katkı sağlayabilir.

Çıkar çatışması/finansal destek beyanı

Bu yazıdaki hiçbir yazarın herhangi bir çıkar çatışması yoktur. Yazının herhangi bir finansal desteği yoktur.

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To cite this article: Cevik B. Histopathologic evaluation and complications of allograft biopsy in renal transplant recipients: In terms of radiologic imaging. Turk J Clin Lab 2020; 4: 307-314.

Orıgınal Article

Histopathologic evaluation and complications of allograft biopsy in renal transplant recipients: In terms of radiologic imaging

Böbrek transplant alıcılarında allograft biyopsisinin histopatolojik değerlendirilmesi ve komplikasyonları: Radyolojik görüntüleme açısından

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ABSTRACT

Aim: Renal transplantation has become the treatment of choice for most patients with end-stage renal disease. Renal allograft biopsy is the most important technique in diagnosis of renal transplant dysfunction. In the light of radiological imaging, we investigated histopathologic evaluation and types and incidence of complications in renal transplant patients.

Material and Methods: In this retrospective study, histopathological biopsy results of patients with renal transplantation who underwent renal biopsy between January 2000 and December 2007 were evaluated in terms of the relationship between calcineurin inhibitor drug level and toxicity development. In addition, biopsy related complications were investigated.

Results: In a total of 386 patients were included in the study and 843 biopsies were performed on these patients. The amount of tissue was adequate in 812 biopsies (96%), inadequate in 6 biopsies (1%) and of limited adequacy in 27 biopsies (3%) for histopathologic evaluation. Acute rejection, tubular epithelial injury and chronic allograft nephropathy were the most frequent diagnoses. Complications of the biopsies were macroscopic hematuria in 4 biopsies (0.5%), perirenal hematoma in 6 biopsies (1%), and arteriovenous fistula in 1 biopsy (0.1%).

Conclusion: Renal biopsy in transplant patients to evaluate the renal allograft dysfunction is a safe method with very low incidence rate of complications.

Keywords: renal transplantation; allograft biopsy; bleeding; arteriovenous fistula

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Recevied: 09.01.2020 accepted: 16.09.2020
Doi: 10.18663/tjcl.672624

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Öz

Amaç: Böbrek nakli, son dönem böbrek yetmezliği olan hastaların çoğunda tercih edilen tedavi yöntemi haline gelmiştir. Renal allogreft biyopsisi böbrek nakli disfonksiyonunun tanısında en önemli tekniktir. Bu çalışmada, radyolojik görüntüleme ışığında renal transplant hastalarında histopatolojik değerlendirme ve komplikasyon tipleri ve sıklığının araştırılması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Ocak 2000 ve Aralık 2007 tarihleri arasında böbrek biyopsisi yapılan renal transplantasyonlu hastaların histopatolojik biyopsi sonuçları, kalsinörin inhibitörü ilaç düzeyi ile toksisite gelişimi arasındaki ilişki açısından değerlendirildi. Ayrıca biyopsi ile ilişkili komplikasyonlar araştırıldı.

Bulgular: Toplam 386 hasta çalışmaya dahil edildi ve bu hastalara 843 biyopsi yapıldı. Doku miktarı 812 biyopside (% 96) yeterli, 6 biyopside (% 1) yetersiz ve 27 biyopside (% 3) sınırlı ancak histopatolojik değerlendirme için yeterli bulunmuştur. Akut ret, tübüler epitel hasarı ve kronik allogreft nefropati en sık konulan tanılardı. Biyopsilerin komplikasyonları 4 biyopside makroskopik hematüri (%0.57), 6 biyopside perirenal hematom (% 1) ve 1 biyopside arteriyovenöz fistül (% 0.15) idi.

Sonuç: Böbrek allogreft disfonksiyonunu değerlendirmek için nakil yapılan hastalarda böbrek biyopsisi çok düşük komplikasyon oranına sahip güvenli bir yöntemdir.

Anahtar Kelimeler: böbrek nakli; allogreft biyopsisi; kanama; arteryo-venöz fistül

Introduction

Renal transplantation has become the treatment of choice for most patients with end-stage renal disease. However, the success of transplantation depends on the preservation of renal graft function. Since the early days of renal transplantation there has been a need for the means of examining allograft tissue in order to diagnose acute and chronic pathological processes in the allograft. Renal allograft biopsy is the most important technique in diagnosis of renal transplant dysfunction [1,2]. The transplant kidney, because of its extraperitoneal and relatively superficial location, is generally suitable for the percutanous needle biopsy approach. Biopsies are performed not only to establish a diagnosis in allografts with deteriorating function but also, using a protocol, to monitor the long-term effects of cyclosporine on the graft, and to detect a recurrence of the original disease in kidney transplant recipients [3].

Hematuria, perirenal hematoma, A-V fistula, pseudoaneurysm, arteriocalical fistula and graft loss can be seen as a complication of biopsy. Major complications reported after biopsies are perinephric or urinary bleeding. Transient microscopic bleeding is common and has no clinical significance [4].

In this study, we aimed to investigate the results of histopathologic evaluation and the types and incidence of complications in renal transplant patients after renal biopsies.

Material and Methods

Patients

Patients who underwent renal allograft biopsies in the Department of Interventional Radiology at Baskent University Hospital between January 2000 and December 2007 were included in the study. We retrospectively analyzed age, gender, donor source, number of transplantations, time passed since transplantation, number of biopsies, date of biopsy, histopathologic evaluation of biopsy, adequacy of specimens, protrombin time before biopsy, serum creatinine levels, complication rates of biopsies, type of calcineurin inhibitor drug, and serum calcineurin inhibitor drug levels. This study was approved by institutional ethical committee. Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

Biopsy procedure

The percutaneous needle biopsy was carried out under ultrasound guidance. The area skin over the transplant was sterilized and draped appropriately. Local anesthetic was injected. The kidney was intended to be punctured in one of the two poles, 18 G/15 cm Ace-Cut (TSK Laboratory, Japan) biopsy needle was advanced until it reached the renal capsule. However, the aim was to restrict the number of needle passes, and only rarely were more than 3 punctures performed. Patients were restricted to bed rest for 6 hours after the biopsy and vital signs were routinely monitored.

Biopsy preparation

Tissue was considered adequate for diagnosis when ten or more glomeruli and two or more arteries were obtained. The tissue was fixed in formalin. Sections cut at 3 to 4 microns were stained with hematoxylin and eosin (HE), Masson's trichome, periodic acid-Schiff (PAS) and methenamine silver. Histopathologic evaluations of biopsies were standardized according to the Banff 97 working classification.

In this retrospective study, we evaluated histopathologic results and complications of biopsy. We also analyzed the patients diagnosed with acute rejection, chronic allograft nephropathy and calcineurin inhibitor drug toxicitiy in biopsies, and we investigated the relationship of acute or chronic calcineurin inhibitor drug toxicity with serum drug levels in renal transplant patients.

Statistical analyses

Data are presented as percentages, mean ± SD, or medians. Statistical analysis was performed using one way ANOVA, Z test, Fisher's exact test, Pearson's correlation or Spearman's rank correlation coefficient. $p<0.05$ was considered as statistically significant.

Results

Totally 386 patients who underwent a total of 843 percutaneous renal allograft biopsies were included in the study. Among patients, 286 were male and 110 were female. The mean age was 37.8 years and ranging between 6 to 71 years.

Gender, donor source, recipient age, sample adequacy and PTZ values in patients with or without complications are summarized in Table 1. There was not any significant difference between patients with or without complications, regarding these parameters.

Table 1: Gender, donor source, recipient age, sample adequacy and PTZ values in patients with or without complications

	Number of biopsies	Number of complications	Complication rate (%)	p-value
gender				0.7414
female	222	12	5.4	
male	621	37	6.0	
Donor supply				0.6966
Cadaver				
	167	8	4.8	
live	676	28	4.1	
Donor age				0.0658
18 y<	12	2	16.7	
18 y≥	831	41	4.9	
Sample proficiency				
sufficient(1)	810	41	5.1	0.1802 (1 -2)
Enough at the border (2)	27	3	11.1	0.3954 (2 -3)
Not enough (3)	6	0	0.0	0.5686 (1 -3)
PTZ Value				0.516
15 sec <	610	35	5.7	
15 sec ≥	118	5	4.2	

Biopsies were performed on the 3rd -9344th days of the transplantation. One-nine biopsies were performed on each transplant kidneys. No increased risk of complications was found with an increasing number of biopsies (Table 2).

The amount of tissue was adequate in 812 biopsies, inadequate in 6 biopsies and of limited adequacy in 27 biopsies for histopathologic evaluation.

Histopathologic evaluations of the biopsies were standardized according to the Banff 97 working classification. Histopathologic evaluation of biopsies were normal in 12 patients, defined as nonspecific changes in 64 patients, borderline changes: suspicious for acute rejection in 90 patients, acute rejection in 274 patients, chronic allograft nephropathy (CAN) in 246 patients, chronic rejection in 7 patients, transplant glomerulopathy in 70 patients, de novo glomerulonephritis/recurrent disease in 48 patients, tubular epithelial injury in 208 patients, acute tubulointerstitial nephritis in 61 patients, chronic tubulointerstitial nephritis in 4 patients, acute tubular necrosis in 20 patients, hemorrhagic necrosis in 5 patients, calsineurin inhibitor drug toxicity in 82 patients, and amyloidosis, tuberculosis, viral, bacterial infection, lipiodozis in 19 patients.

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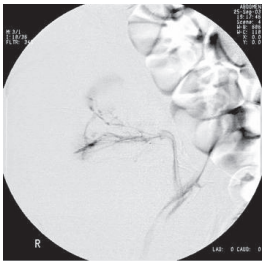
Table 2. Frequency of complications in relation to the number of biopsies performed per transplant

No. transplants	Biopsies	Complications n	(%)
166	1	4	2.4
105	2	2	1.9
55	3	11	20.0
31	4	10	32.3
12	5	1	8.3
17	6-9	6	35.3

Complications of the biopsies were macroscopic hematuria in 4 biopsies, perirenal hematoma in 6 biopsies, arteriovenous fistula in 1 biopsy. Arteriovenous fistula was treated with coil embolization. None of the patients with macroscopic hematuria required blood transfusion. None of the patients were expired due to the graft following biopsy.

Some cases are summarized below:

Case 1. An abdominal CT was performed on 26-year-old man following hemoglobin decrease after renal transplant biopsy. Retroperitoneal hematoma was revealed on CT. Renal and pelvic angiography was performed. Angiography demonstrated contrast agent leak from interlobar renal artery in kidney transplantation. Leak was treated with microcoil and histoacryl-lipiodol embolization (Figure 1A-B-C).



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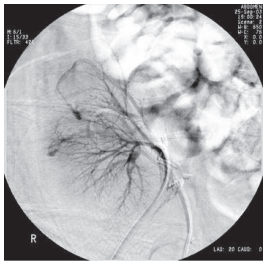

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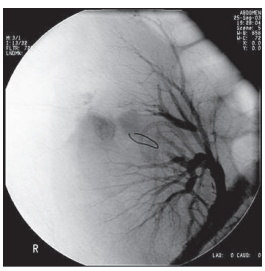
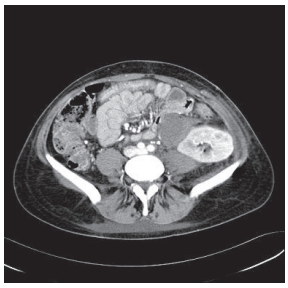


Figure 1 A-B-C: Angiography demonstrated contrast agent leak from interlobar renal artery in kidney transplantation. Leak was treated with microcoil and histoacryl-lipiodol embolization

Case 2. In a 25-year-old woman patient, hemoglobin decreased following renal transplant biopsy. Abdominal CT was performed. CT revealed perirenal hematoma in renal transplant (Figure A-B). After six month, A-V fistula was suspected in US. Renal angiography demonstrated A-V fistula in inferior pole of renal transplant. A-V fistula was treated with multiple coil embolization (Figure 2C-D-E).



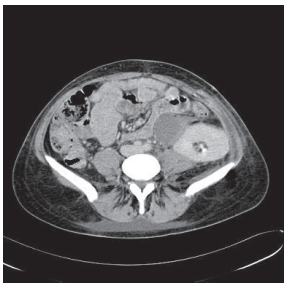
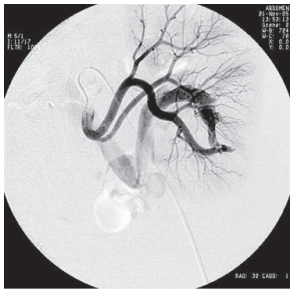


Figure 2 A-B: Abdominal CT revealed perirenal hematoma in renal transplant (Figure A-B).



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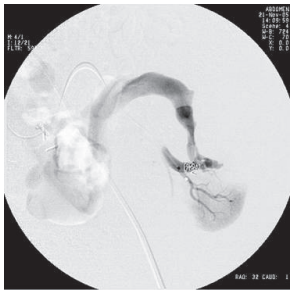

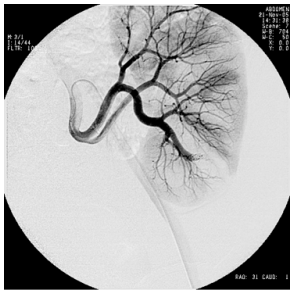

Figure 2 C-D-E: Renal angiography demonstrated A-V fistula in inferior pole of renal transplant. A-V fistula was treated with multiple coil embolization (Figure 2C-D-E).

Case 3. 53-year-old woman with renal transplant developed left quadrant pain and decrease in hemoglobin levels following renal transplant biopsy. Abdominal CT was performed. CT revealed perirenal subcapsular hematoma (Figure A), defect and lacking contrast media in inferior pole of transplant kidney (Figure B). During operation, the surgeons detected three lacerations in the transplanted kidney (Figure C). Then the surgeons performed packing with Surgicell and 2 unit ES and one unit fresh frozen plasma was given to the patient.

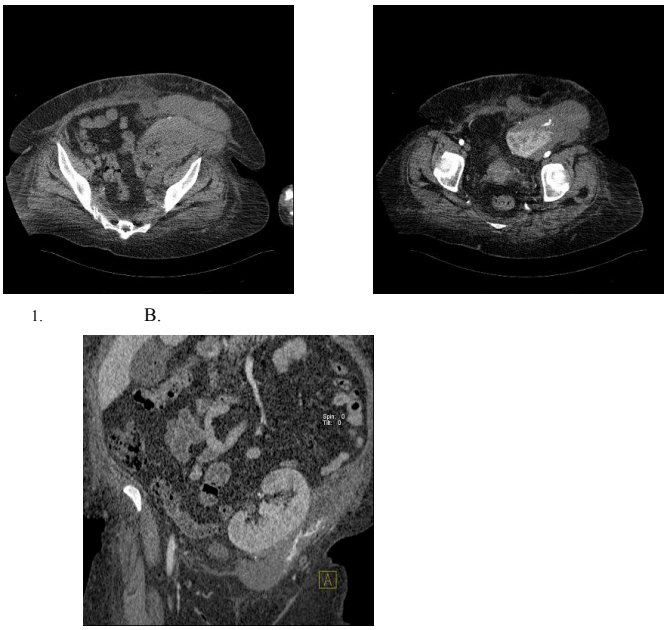

Figure 3 A-B-C: Abdominal CT revealed perirenal subcapsular hematoma (Figure A), defect and lacking contrast media in inferior pole of transplant kidney (Figure B). During operation, the surgeons detected three lacerations in the transplanted kidney (Figure C).

Case 4. 35-year-old woman patient's hemoglobin level decreased following transplant biopsy. Abdominal CT showed contrast-enhanced extravasation compatible with active hemorrhage and hematoma extending from the posteriomedial transplant kidney to the pelvis (Figure 20 A-B). The patient received 400 units / hour heparin infusion. 4 units of TDP and 2 units of ES were given. Then she was operated and hematoma was evacuated.

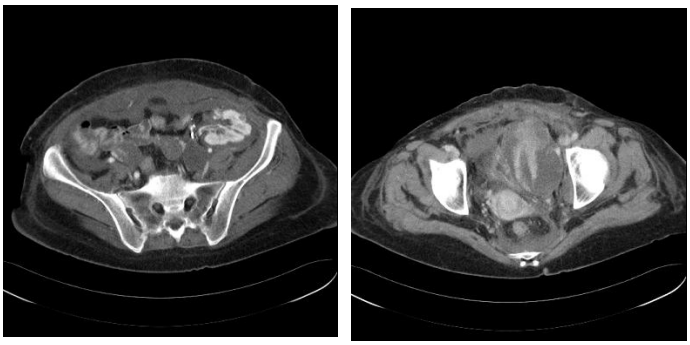

Figure 4 A-B: Abdominal CT showed contrast-enhanced extravasation compatible with active hemorrhage and hematoma extending from the posteriomedial transplant kidney to the pelvis (Figure 4 A-B).

Case 5: A 42-year-old male patient complained of right lower quadrant pain and decreased hemoglobin levels in the follow-up after transplant kidney biopsy. Abdominal CT examination showed a parenchymal defect in the posterior of the right kidney iliac fossa and a contrast agent extravasation compatible with active hematoma extending to the pelvis and retroperitoneal space (Figure 5). Thereafter, three units of TDP were administered. He was operated and hematoma was evacuated.

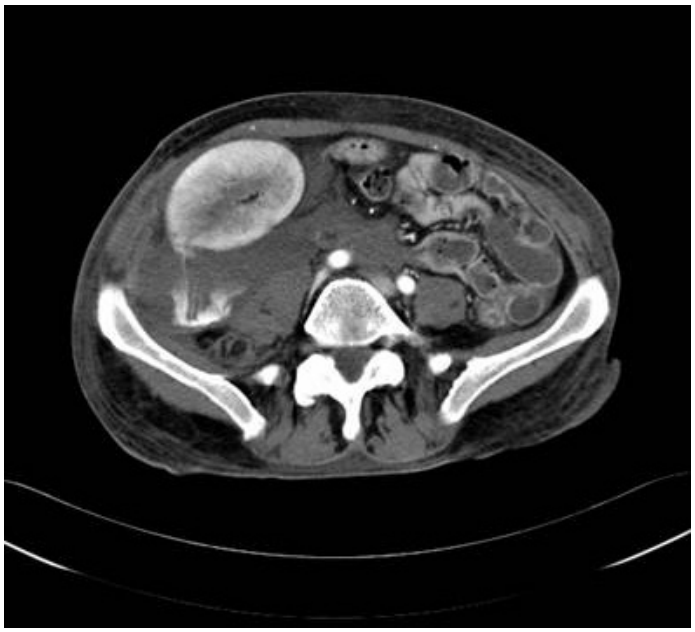

Figure 5: Abdominal CT examination showed a parenchymal defect in the posterior of the right kidney iliac fossa and a contrast agent extravasation compatible with active hematoma extending to the pelvis and retroperitoneal space

Case 6: A 56-year-old male patient underwent Doppler US examination after a transplanted kidney biopsy, and a hematoma in the left lateral iliac fossa was seen in the adjacent kidney, and a 14 F drainage catheter was placed in our interventional radiology unit. Then, a CT scan of the left iliac fossa revealed a hematoma adjacent to the transplanted kidney and a drainage catheter (Figure 6).

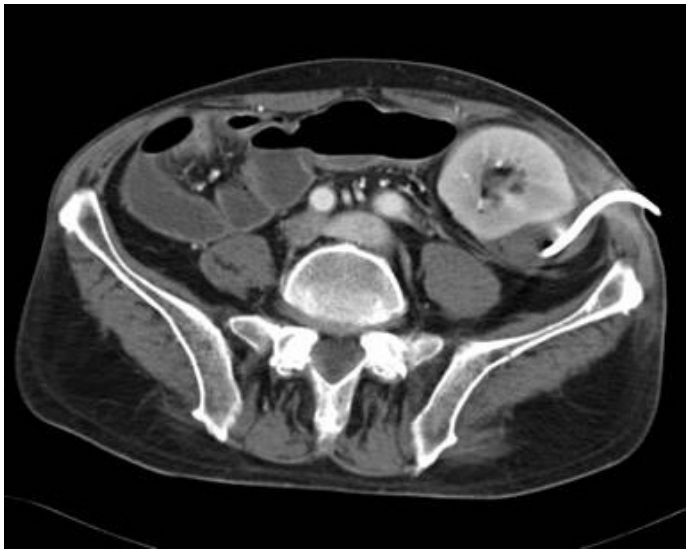

Figure 6: CT scan of the left iliac fossa revealed a hematoma adjacent to the transplanted kidney and a drainage catheter

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Calcineurin inhibitor drug toxicity was detected in 82 of the biopsies. Cyclosporine was used as the calcineurin inhibitor drug in 52 of these biopsies and tacrolimus was used in 30 of these biopsies. Cyclosporine levels detected during biopsy were 65-800 ng / ml (normal value 100-400 ng / ml) with a mean of 254.3 ng / ml, and tacrolimus level was 5-32 ng / ml (normal value 5-20 ng / ml). and a mean of 12.2 ng / ml. The effect of drug levels on the development of acute or chronic toxicity in calcineurin inhibitory drug users is shown in Table 3. There was not a significant relationship between low or high serum drug levels and toxicity development.

Table 3: Effect of drug level on the development of acute or chronic toxicity in calcineurin inhibitor drug users

	Number of patients using calcineurin inhibitor		
Calcineurin Inhibitor Drug Level	Cyclosporine (ST)	Tacrolimus (TT)	Total
Low (ST<400. TT<20)	49 %94.2	26 %86.7	75
High (ST>=400. TT>=20)	3 %5.8	4 %13.3	7
Total	52	30	82
Fisher exact test p-value =0.253			

Discussion

The most objective method for obtaining renal allograft pathologies is histopathological examinations performed by biopsy [1,2]. Therefore, allograft biopsy is currently the most reliable method for examining allograft dysfunction. Although it is an invasive method, the reason for its high rate of application is the lack of an alternative physical examination or laboratory examination. Although both clinical and other laboratory findings are very useful in reaching the diagnosis, they are insufficient to provide the information that the biopsy provides.

Non-invasive methods including; examination of peripheral T cells, lymphocyte activation markers, serum and urine cytokine levels and invasive methods including; fine needle aspiration and monoclonal antibody techniques could not replace biopsy even if diagnosis was used in renal allograft dysfunction [3,5]. Therefore, biopsy and histopathological examination have been accepted as the gold standard especially in allograft dysfunction. By evaluating the clinical findings together with biopsy, the status of the graft is best understood and some pathologies which are very difficult to differentiate with clinical findings are clarified. For example, allograft biopsy will provide the possibility to differentiate the pathologies such as cyclosporine toxicity and acute rejection and predict the graft survival, which may give the same findings as clinical investigations but treatment approaches are completely different [6].

Since the transplanted kidney is located under the abdominal muscles in the iliac fossa, it is suitable for percutaneous biopsy. US guided application increases the success of biopsy [7]. In our study, the histopathologically sufficient tissue access rate was satisfactory. Only 6 out of 843 biopsies showed insufficient material. Our success rate was calculated as 99.3%. In some series it is reported in proportions similar to ours [8]. US-guided biopsy was done to be effective in both to obtain the active tissue and decrease the risk of complications. In some studies, especially in rejection cases that can be treated, false negative results have been shown to decrease from 1% to 10.5% by performing two punctures and taking two samples [9]. The classification of histopathological examination was performed according to Banff classification, which has been studied in recent years and aimed to achieve a significant standardization by nephropatologists [10].

It was remarkable that the number of biopsies in our series was quite high. As the risk of complications decreased to negligible levels with imaging techniques, biopsy indications in transplanted patients have been expanded considerably. In addition, protocol biopsies have been proposed at certain times in order to determine the future graft survival or to detect subclinical acute rejection attacks. In some studies, it has been shown that especially protocol biopsies to be performed in the early period may affect subclinical rejection attacks that may adversely affect graft survival and are not reflected in laboratory findings [11]. In the study of Mao et al., it was emphasized that post-transplant biopsy performed at 1 month provides important clinical information in detecting pathologies and predicting graft survival as the risk factors for long-term graft survival [12]. This approach may be very invasive. However, it should be kept in mind that biopsy provide important information that may affect patient and graft survival in the presence of proper indication. In our study, biopsy was not performed in patients without any problem related to allograft functions.

Percutaneous kidney biopsies can be performed using 14 G, 16 G or 18 G, automatic or semi-automatic needles. In a study, it was reported that three different thickness needles can be used safely in renal allograft biopsy and there was no difference in terms of adequate tissue sample while pain complaints

were found more in those who underwent biopsy with a 14 G needle [13]. In another study, US guided biopsies with 18 G needles and 14 G needles without US guidance were compared in terms of complication and tissue sample adequacy and no significant difference was found [14]. In a study comparing the 18 G needle with 14 G, Boyvat et al, reported that tru-cut needle biopsy techniques have obtained enough tissue samples and found that there are fewer complications [15]. In our study, 18 G Ace-cut automatic needle was used and it was very successful in obtaining adequate tissue sample and low complication rate.

Hematuria, perirenal hematoma, A-V fistula, pseudoaneurysm, arteriocalical fistula and graft loss can be seen as a complication of biopsy [16]. The rate of asymptomatic microscopic hematuria to varying degrees after native kidney biopsies is 100% [17]. Therefore, it is not considered as a complication since it is a natural result of renal puncture. Transient macroscopic hematuria may occur and often regress by itself [7]. However, it may rarely require blood transfusion. The incidence of gross hematuria was 5-7% in transplant and native kidneys [3]. Blood transfusions were not required in 4 of our patients who developed macroscopic hematuria and hematuria regressed spontaneously.

There was no significant difference between the patients who developed complications, whether the age was less than 18 years or older, whether the donor source was cadaver or alive, the PTZ value was higher or lower than normal, and adequate or insufficient tissue samples were obtained. In a study conducted by Wilzeck et al., it was found that performing biopsy early or late after transplantation and normal or abnormal renal function did not differ in terms of complications [8]. In contrast, patients with acute vascular rejection had a higher risk of bleeding complications. This is thought to be mainly due to vascular fragility caused by inflammatory vascular changes in the transplant [8]. In our study, acute rejection in 2 patients, border-line changes in 1 patient, acute calcineurin inhibitory toxicity in 1 patient and tubule epithelial injury in 2 patients were detected. Another common complication after renal needle biopsies is the A-V fistula, and most traumatic fistulas spontaneously close in 1 to 18 months In one of our patients, A-V fistula was detected in the transplant kidney 6 months after biopsy and coil embolization treatment was applied. Graft loss is one of the major complications. The causes of graft loss due to excessive bleeding seen in the study of Wilzeck et al. were acute vascular rejection, and renal vein thrombosis, due to deep and excessive penetration of the kidney including not only the cortex but also the medulla [8].

In our study, and the only major complication was perirenal hematoma in 6 biopsies and A-V fistula in 1 biopsy. Large numbers of biopsy series in the literature have also reported low numbers of complications similar to our series. For example, in two large series of 1129 and 1390 biopsies, mortality was absent and graft loss was reported to be only 0.3% and 0.4% [8,18].

In our study, one of the most common histopathological diagnosis was CAN (chronic allograft nephropathy). Chronic allograft nephropathy is histopathology characterized by chronic changes in the arteries, interstitium, tubules and glomeruli. The development of CAN in the transplant kidney is associated with progressive loss of function and subsequent loss of graft.

Calcineurin inhibitors used in immunosuppressive therapy in renal allograft are CycA and tacrolimus. Calcineurin inhibitor drugs are nephrotoxic, and may cause acute or chronic toxicity. There are also studies suggesting that drug level is associated with toxicity and may cause CAN and graft loss in the future [20]. In our study, there was no relationship between acute and chronic toxicity and drug levels in tacrolimus and CycA groups. Histopathological findings of toxicity were observed even in patients with normal drug levels.

In the study of Liptak et al., the serum levels of these drugs do not correlate well with the extent of renal damage caused, and the clinical manifestation is nonspecific [21].

Conclusion

Biopsy performed to evaluate the renal allograft dysfunction in renal transplant patients is safe and the incidence of complications is significantly low. There is no correlation between developing acute or chronic calcineurin inhibitor drug toxicity with serum drug level.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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To cite this article: Gunaydin S, Budak AB, Gunertem OE, Tumer NB, Kunt AT, Ozisik K. Comparative efficacy of long-term anticoagulation in patients with acute deep vein thrombosis treated with pharmaco-mechanical catheter-directed thrombolysis. Turk J Clin Lab 2020; 4: 315-322.

Orıgınal Article

Comparative efficacy of long-term anticoagulation in patients with iliofemoral acute deep vein thrombosis treated with pharmaco-mechanical catheter-directed thrombolysis

Farmakomekanik kateter aracılı tromboliz ile tedavi edilen akut ilyofemoral derin ven trombozlu hastalarda uzun süreli antikoagülasyonun karşılaştırmalı etkinliği

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ABSTRACT

Aim: We aimed to compare the stability of pharmacologic profile, rate of symptomatic recurrent venous thromboembolism, major bleeding and the net clinical benefit on the regimen with vitamin K antagonist (VKA), low molecular weight heparin (LMWH) and direct oral anticoagulant (DOAC) for long-term anticoagulation in patients undergoing pharmaco-mechanical catheter-directed thrombolysis (PMCDT) for the treatment of deep vein thrombosis (DVT).

Material and Methods: During the period from January 2019 until June 2019, data of 112 patients who underwent PMCDT for the treatment of acute iliofemoral DVT in our institution with long-term apixaban (Pfizer, Turkey) medication were prospectively collected (Group 1-DOAC). Data of control groups within January 2017- December 2018 period were collected retrospectively. Control groups consisted of PMCDT patients with extended LMWH (Tinzaparin, Abdi Ibrahim Pharma, Turkey) treatment (Group 2-LMWH; N=119) and with VKA (Coumadin, Eczacibasi Pharma, Turkey) treatment (Group 3- Control; N=111). Results: Patients treated with VKA showed a significant incompliance starting from third month up to one year. Patency rate diminished significantly below 70%. 32% of VKA patients were out of therapeutic range even in the first month leading to 40% at the end of the year. Likert Scale, Villalta/VCCS and VEINES-QOL-Sym scores confirmed the clinical data.

Conclusion: This study highlights the potential role of DOAC as a reasonable alternative to VKAs/LMWH in the long-term anticoagulation strategy for DVT. We await larger clinical trials to support these findings and establish the role of DOAC as the standard of care for patients with DVT.

Keywords: deep vein thrombosis; venous thromboembolism; pharmaco-mechanical catheter-directed thrombolysis; vitamin k antagonists; low molecular weight heparin; direct oral anticoagulants

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Recevied: 04.03.2020 accepted: 11.08.2020
Doi: 10.18663/tjcl.796973

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Öz

Amaç: Derin ven trombozu (DVT) tedavisi için farmakomekanik kateter aracılı trombliz (FMKAT) yapılan hastalarda; vitamin K antagonistlerini(VKA), düşük molekül ağırlıklı heparini (DMAH) ve direk oral antikoagülan ajanları (DOAK) farmakolojik profilllerinin stabilitesine, semptomatik rekürren venöz tromboembolik, major kanama ve klinik fayda oranlarına göre karşılaştırmayı hedefledik.

Gereç ve Yöntemler: Ocak 2019 ile Haziran 2019 tarihleri arasında kliniğimizde akut iliofemoral DVT tanısı ile FMKAT yapılan ve uzun dönemde apiksaban (Pfizer, Türkiye) tedavisi ile takip edilen 112 hastanın verileri toplandı. (Grup 1- DOAK) Kontrol gruplarının dataları ise Ocak 2017 ile Aralık 2018 tarihleri arasında yine kliniğimizde akut iliofemoral DVT tanısı ile FMKAT yapılan ve uzun dönemde DMAH (Tinzaparin, Abdi Ibrahim İlaç, Türkiye) tedavisi (Group 2-DMAH; N=119) ve VKA(Coumadin, Eczacibasi İlaç, Türkiye) tedavisi (Grup 3- Kontrol N=111) hastalardan toplandı.

Bulgular: VKA tedavisi ile takip edilen hastalarda 3.aydan başlayıp 1 yıla kadar ki takip sürelerinde belirgin oranda tedaviye uyumsuzluk saptandı. Patensi oranları %70'in altındaydı. VKA hastalarının %32'si yıl sonunda terapötik dozlarda değildi. Likert skalaları, Villalta/VCCS ve VEINES-QOL-Sym skorlama sistemlerinin sonuçları klinik sonuçlar ile uyumluydu.

Sonuç: Bu çalışma DOAK'ların DVT hastalarında tedavi için DMAH ve VKA'lara uygun bir seçenek olduğunu gösterdi. DOAK tedavisinin DVT hastalarında standart bir tedavi olarak tercih edilebilmesi için bizim elde ettiğimiz sonuçları destekleyecek geniş kapsamlı klinik çalışmaların sonuçları beklenmektedir.

Anahtar kelimeler: derin ven trombozu; venöz tromboembolizm; farmakomekanik katater araçılı tromboliz; vitamin k antagonistleri; düşük molekül ağırlıklı heparin; direk oral antikoagülanlar

Introduction

Venous thromboembolism (VTE), which comprises deep venous thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of morbidity and mortality worldwide.

Standard treatment of VTE, using low-molecular-weight heparin (LMWH) overlapped with vitamin K antagonists (VKAs), is effective but requires frequent laboratory monitoring and has the potential for multiple drug and dietary interactions. In recent years, novel treatment strategies with direct oral anticoagulants (DOACs) have been increasing in popularity and availability [1,2].

Post-thrombotic syndrome (PTS) is a chronic complication of DVT, which develops in 20% to 50% of patients. PTS arises from a combination of venous outflow obstruction, venous hypertension, valvular incompetence, and secondary calf muscle pump dysfunction leading to ambulatory venous hypertension. PTS results in substantially increased healthcare costs and significantly impaired quality of life. Little is known about effects of different anticoagulants on PTS development [3].

Several studies have shown that average patients spend more than 20 % of their time below the therapeutic range during treatment with VKA. It is confirmed that the therapeutic intensity of VKA treatment is an essential determinant for development of PTS since the time spent beneath the therapeutic range is associated with PTS development [4-6]. Furthermore, a systematic review found a significantly lower rate of PTS in patients treated with LMWH alone compared to patient treated with LMWH followed by VKA [7].

DOACs approved for treatment of VTE have a stable pharmacological profile and thereby could overcome the disadvantages of VKA. However, the risk of PTS in DVT patients treated with DOACs is unknown [8].

Pharmaco-mechanical catheter-directed thrombolysis (PMCDT) refers to mechanical thrombus disruption concomitant with fibrinolytic therapy, offering a lower dosage of thrombolytic agent, a shorter procedure and an improvement in outcomes. PMCDT is an alternative option for treatment of DVT and decreasing the incidence of PTS. The patients who are most likely to benefit have iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy of >1 year, and a low risk of bleeding. More rapid thrombus resolution is associated with the improved valvular function [9-10].

Long-term treatment is preconized in a significant proportion of the patients with VTE. However, limited direct/indirect comparisons are available to appropriately weight the benefit/risk ratio of the diverse treatments available.

We aimed to compare the stability of pharmacologic profile,

rate of symptomatic recurrent VTE, major bleeding (MB) and the net clinical benefit on VKA, LMWH and DOAC for extended anticoagulation. We chose patients undergoing PMCDT for treatment of DVT, since it is verified to clean all thrombus load by angiography/ultrasound at the end of the procedure and start comparison of three pharmacologic regimens in totally cleaned DVT confirmed at baseline.

Material and Methods

The study was approved by Clinical Research Ethics Committee of Numune Training & Research Hospital, Ankara- Turkey (25.04.2018/1917). Patient informed consent forms were collected in all cases.

Study Design and Patient Selection

During the period from January 2019 until June 2019, data of 112 patients who underwent PMCDT for the treatment of acute iliofemoral DVT in our institution with long-term apixaban (Eliquis, Pfizer, Turkey) medication were prospectively collected (Group 1-DOAC). Data of control groups within January 2017-December 2018 period were collected retrospectively. Control groups consisted of PMCDT patients with extended LMWH (Tinzaparin-Innohep, Abdi Ibrahim Pharma, Turkey) treatment (Group 2-LMWH; N=119) and with VKA (Warfarin-Coumadin, Eczacibasi Pharma, Turkey) treatment (Group 3- Control; N=111).

The use of propensity score matching addressed treatment selection bias. Patients were matched by propensity score for age, gender, BMI, and Wells score to have 75 patients in each group.

Inclusion criteria included acute presentation (<14 days), phlegmasia cerulea dolens, extensive proximal DVT + femoropopliteal DVT, life-expactancy > 1 year and low risk of bleeding. Exclusion criteria consisted of low life expectancy (terminally ill patients), renal failure (GFR < 60 mL/min), contraindication to anticoagulation or tPA, isolated femoro-popliteal DVT, subacute (14-28 days) or chronic (>28 days) DVT, severe dyspnea or severe acute medical illness precluding safe procedure, asymptomatic DVT, active gastrointestinal bleeding, stenosis needing stent, success rate <90%, in-hospital recurrent event and malignancy.

All patients were symptomatic upon admission and after calculating the Wells score [11], venous duplex ultrasonography was performed for initial diagnosis. The extent of the thrombus and the calculation of the Marder score [12] was evaluated and calculated by initial contrast venography.

Technique (PMCDT)

All procedures were performed under local anesthesia in single-session in the angio-suite and all vascular interventions were performed under doppler ultrasound guidance. A retrievable thrombolysis catheter with VCI filter (TPSTM, Thrombolysis Catheter, 50 cm, 30 mm filter diameter, 8F, Invamed, Ankara, Turkey) was placed caudal to the renal vein origins via contralateral common femoral vein. Then an ipsilateral retrograde approach via popliteal vein or posterior tibial vein was accessed, and a 7F introducer sheath was inserted.

Percutaneous mechanical thrombectomy device (MantisTM 7F, 90 cm, Invamed, Ankara, Turkey) was inserted, activated and advanced in an antegrade fashion. In every 3- to 5- minute, PMCDT was temporarily deactivated and withdrawn. The macerated thrombus materials and residual thrombolytic agents were suctioned by the help of an automatic aspiration system (Dovi aspiration thrombectomy device, 8F, 90 cm, Invamed, Ankara, Turkey) that was advanced over a 0.035-inch guidewire. A suitable multiple-side-hole infusion catheter (ViperTM, Invamed, Ankara-Turkey) was placed within the thrombosed vessel with the aid of fluoroscopy. The mixture of tissue plasminogen activator

(rtPA, Actilyse, Boehringer Ingelheim, Germany) and saline (1:10) was infused into the residual thrombus.

Before start, ascending venography was obtained to examine the extent and location of the thrombus and to calculate the Marder score. The mixture of rtPA and saline administered in every 5- to 10 cm interval through the device's side injection port as rotational thrombolysis and rtPA delivery were used simultaneously.

Based on venography, the remaining residual stenosis of less than 10% was considered as successful recanalization. When post-treatment venography revealed any underlying stenotic lesion of the affected vessels, balloon angioplasty (PTA) was performed via a 10–12 mm–diameter balloon to ensure adequate flow.(n=24) Thrombus removal, patency of the iliofemoral vein, and thrombi in the filter were confirmed by venography assessment.

Patients were transferred to the inpatient service post-procedurally. For all cases, ViperTM catheter was left in the lumen and 10-15 mg rtPA mixture with saline was administered as continuous infusion to eliminate residual thrombus load or thrombus remnants behind the venous valves (40 mg maximum dose). During catheter directed thrombolysis, routine monitoring of plasma fibrinogen (FIB) concentration, activated partial thromboplastin time and platelet count were performed. When the FIB level was 1.0 to 1.5 g/L, the rate of drug administration was slowed down; when the FIB was <1.0 g/L, thrombolysis was temporarily paused. TPSTMcatheter was retrieved in every patient on postprocedural 2nd day after

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a venographic evaluation of the filter whether any thrombus caught inside. Hospital stay time, Marder score, the immediate procedural success rate were recorded.

Medical Therapy

Patients were started administration of tinzaparin (subcutaneously once daily at a fixed dose, determined according to three weight categories: 45–49 kg (5000 IU); 50–70 kg (7500 IU); 71–100 kg (10,000 IU) as soon as they were hospitalized [13].

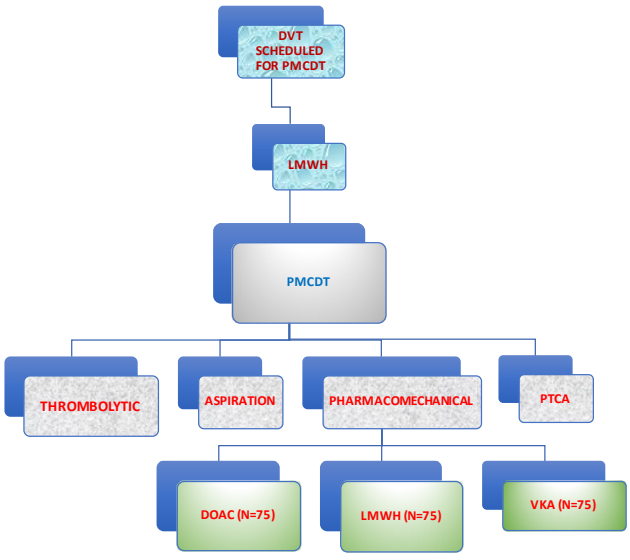
At the end of the procedure, patients received one of the three regimens before discharge.

Group 1: apixaban 2x5 mg (Therapeutic dose range- Anti-Xa Activity: 1.0-2.0 U/mL)

Group 2: Tinzaparin, single daily injection (dosing with respect to body weight) (Therapeutic dose range- Anti-Xa Activity: 1.0-2.0 U/mL)

Group 3: VKA (Therapeutic dose range- international normalized ratio-INR: 2-3)

All patients used thigh-high elastic compression stockings, providing from 30 to 40 mmHg of pressure, for 6 months. Patient flow chart is represented in Fig 1



Follow-up and Outcome Assessments

All patients were evaluated before discharge and were scheduled to return for ambulatory follow-up visits at 1, 3, 6 and 12 months after the procedure except for an emergency. At these visits, physical examination, doppler ultrasonography, INR (VKA patients) and anti-Xa (LMWH and DOAC patients) levels were performed.

Definitions of major and minor complications, anatomical success, early and late re-thrombosis, recurrent DVT, anatomical patency were evaluated within the scope of Reporting Standards for Endovascular Treatment of Lower Extremity Deep Vein Thrombosis [14].

Early symptom relief, was evaluated by assessing leg swelling using standardized leg circumference measurement through 10 cm below the tibial tuberosity of the index leg and leg pain using a 7-point Likert Scale which both instruments were previously reported as effective and inexpensive to document changes in limb symptomatology [14].

PTS was assessed by the Villalta Scale [15] that classifies PTS as absent (score 0–4), mild (score 5–9), moderate (score 10–14), or severe PTS (score ≥15, or presence of ulcer) and VCSS which grades the severity of PTS as absent (score 0- 3), mild to moderate (score 4-7), and severe (score > 8) [16]. Villalta and VCSS scores were calculated at 6th, and 12th -month controls.

To grade the severity of chronic venous disease and its impact on QOL, Venous Insufficiency Epidemiological and Economic Study Quality of Life measure (VEINES-QOL) evaluation were performed at 12th -month control [17].

Statistical analysis

All statistical analyses were conducted using SPSS 18.0 software (version 18.0; SPSS, Chicago, Illinois). Continuous data were reported as means +standard deviation, and the significant difference was verified using student t test. Categoric variables were expressed as frequency and percentages. Nominal data including clinical characteristics and predisposing factors were reported as the number of subjects and were analyzed using Wilcoxon-Mann-Whitney test. Venous patency and re-occlusion rates during follow-up were demonstrated by Kaplan-Meier analysis. Statistical significance was defined a P value of <0.05.

Results

Baseline evaluation of patients on hospitalization is summarized in Table 1.

Early peri-procedural data is listed in Table 2.

Table 1: Baseline characteristic of patients upon admission

	Group 1 (DOAC) (N=75)	Group 2 (LMWH) (N=75)	Group 3 (VKA) (N=75)
Age	57.1±15	52.6±15	50.4±15
Gender (F/M)	44/31	40/35	39/36
BMI (kg/m2)	29.2±8	30.4±10	28.7±9
Wells Score*	5.7±1.5	5.5±1.5	5.8±1.5
Duration of Symptoms (day)	6.4±2	7.3±3	5.9±2
Likert Score >5 #	48	52	57

F/M: female/male BMI: Body mass index
*:Wells Clinical DVT model: A score of 3 or higher indicates a high risk of DVT
#: Leg pain severity measured by Likert Scale

Table 2: Early peri-procedural data

	Group 1 (DOAC) (N=75)		Group 2 (LMWH) (N=75)		Group 3 (VKA) (N=75)	
Procedure Duration (min)	56.8±22		59.6±25		60.2±25	
Post-procedural full patency (%)	94.7±5		92.5±5		97.4±5	
Marder Score (Before/After)	11.4±3	2.3±1	13.6±4	2.5±1	10.9±3	2.1±1
Hospital Stay (day)	2.4±1.1		2.5±1.2		2.0±1.2	

No complications occurred in terms of pulmonary embolism or bleeding during early period. Minor bleeding as subcutaneous hemorrhage at the access site was observed in 2, 3 and 2 patients in Groups 1,2 and 3 respectively.

Follow-up data of patients is documented in Table 3. 4 patients in DOAC group were excluded for not being able to complete 12- month data.

Discussion

The use of VKAs like warfarin is recommended by guidelines in the medical treatment of VTE. However, it is limited by the need for frequent monitoring of INR, drug interactions, drug-food interactions, prior bridging with inpatient parenteral anticoagulation before commencing, as well as the risk of bleeding with its use [18]. Conversely, DOAC does not require regular INR testing and dose adjustments, while still remaining effective and safe in the treatment of VTE, with comparable rates of clinically significant bleeding and mortality [6]. While anticoagulation probably plays an important role, evidence-based data is scarce and optimal anticoagulation treatment of DVT to prevent PTS development is still unknown. In treatment with VKAs, sub-therapeutic anticoagulation in the first few weeks is associated with a higher incidence of PTS development. Analysis of long-term LMWH treatment alone showed a lower incidence of PTS compared to standard treatment with warfarin.9 Together with the observation that the severity of symptoms and signs four weeks after acute DVT is associated with subsequent PTS development, these findings suggest optimal anticoagulation treatment in the first weeks after acute DVT is crucial in preventing the development of PTS later in the course of the disease [19].

Sub-therapeutic anticoagulation might maintain thrombin production, thus promoting coagulation, reducing natural clot lysis and causing venous wall damage, which could lead to PTS development in the long-term. Therefore, DOAC, with their rapid onset and stable pharmacokinetics, could lower the incidence of PTS in comparison to warfarin [20-21].

We designed this study comparing three different regimens after PMCDT, in which patients were completely (>90%) cleaned from the existing thrombi load verified by ultrasonography and venography and continued a thorough follow-up to one year.

As demonstrated in Table 3, our patients treated with VKA showed a significant incompliance starting from third month up to one year. It is known that patients treated with VKA and monitored in a community setting have a lower adherence than patients in a trial setting. Considering that reduced treatment burden and regimen complexity are associated with better compliance, DOAC patients might have a better adherence in clinical practice and thereby contributing to better long-term clinical outcomes like PTS, especially in settings where INR control is suboptimal [22-23].

Patency rate diminished significantly below 70%. Major

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Table 3: Long-term follow-up of patient groups

	GROUP 1 -DOAC (N=71)				GROUP 2- LMWH (N=75)				GROUP 3-VKA (N=75)			
	1st Month	3rd Month	6th Month	12th Month	1st Month	3rd Month	6th Month	12th Month	1st Month	3rd Month	6th Month	12th Month
RECURRENCE (N)	2	3	2	3	3	4	3	4	3	5	5	4
DRUG-RELATED INCOMPLIANCE (N)	0	4*	1**	6*	6	7	9	7	2	11	10	11
MINOR BLEEDING (N)	0	5	5*	6*	2	6	9	9	5	10	14	13
MAJOR BLEEDING (N)	0	1	5	4*	3	3	7	6	2	4	8	8
INR OUT OF THERAPEUTIC RANGE (N)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	24	10	13	29
ANTI-Xa OUT OF THERAPEUTIC RANGE (N)	2	3	3	5	1	4	4	8	N/A	N/A	N/A	N/A
PATENCY RATE (%)	90±5	88±5	83±5	80.5±5*	91±5	82±5	77±5	70±4	94±5	80±5	73±4	68±4
REHOSPITALIZATION (N)	0	0	1	1*	0	0	2	1*	4	2	2	5
LIKERT SCALEμ	1.81 ± 0.1	2.1 ± 0.1	2.9 ± 0.12	3.2 ± 0.1	1.9 ± 0.1	3.2 ± 0.1	4.9 ± 0.2	5.2 ± 0.3μ	1.77 ± 0.1	3.7 ± 0.1	5.3 ± 0.3μ	6.8 ± 0.5μ
VILLALTA SCORE#			4.1 + 4	5.8 + 4			10.1 + 5	14.8 + 6			12.4 + 5	16.8 + 6#
VCCS>			3.6 + 1.7	5.8 + 4			7.88 + 3	9.3 + 4>			8.94 + 4>	10.5 + 5>
VEINES-QOL-Sym SCOREδ				61 + 10**				41 + 10δ				38 + 8δ

*: statistically significant vs control (Group 3)
**: statistically significant vs Group 2 and control (Group 3)
N/A: not applicable
μ: Leg pain severity measured by Likert Scale (>5 significant)
#: Villalta Score (>15, significant: Severe Post-thrombotic syndrome)
>: VCCS (>8, significant: Severe Post-thrombotic syndrome)
δ: VEINES-QOL-Sym (Venous Disease Specific- Quality of Life)

bleeding episodes were prominent in the late post-procedural period leading to more significant hospitalization.

32% of VKA patients were out of therapeutic range even in the first month leading to 40% at the end of the year. During the Einstein DVT trial, enoxaparin/VKA patients were 21 % of the time below the therapeutic range (INR 2–3) and more than 90 % of the patients in both rivaroxaban and enoxaparin/ VKA-treated patient had a compliance rate of 80 %.

Likert Scale and Villalta/VCCS scores confirmed the clinical data. VEINES-QOL-Sym score was significantly better in DOAC group with respect to VKA in 6th and 12th month controls and LMWH in 12th month controls, demonstrating better quality of life.

Our study has also some limitations. The main limitation of the study was the retrospective nature of the study which we tried to balance with propensity score matching.

The majority of PMCDT procedures in studies including our study were performed via popliteal approach. This approach has a possibility to leave a burden of residual occlusive thrombus in the popliteal vein, thereby leading to a possible increment in symptoms of PTS. We could have designed another group studying posterior tibial access to compare. Residual thrombus load and the patency of outflow veins were evaluated by venography in our study. But we know that, assessment of the patency of iliofemoral veins should be based on IVUS rather than venograms alone, because even small amounts of thrombus may enhance inflammatory reaction and thereby cause recurrent DVT and/or PTS. Due to reimbursement criteria in our country, we could not use IVUS in our study.

Conclusion

Our study highlights the potential role of DOAC as a reasonable alternative to VKAs/LMWH in the long-term anticoagulation strategy for DVT. DOAC appears to be similar in efficacy, and may potentially result in fewer major bleeding events, rehospitalization, better compliance and stability in therapeutic range leading to better quality of life. This is one of the first reports comparing three popular regimens in the setting of PMCDT. We await larger clinical trials to support these findings and establish the role of DOAC as the standard of care for patients with VTE.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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To cite this article: Ayhan İ, Çam SA, Uysal F, Arslan SO. Yağ asidi kompozisyon değişikliklerinin kalp damar hastalıkları açısından önemi. Turk J Clin Lab 2020; 4: 323-333.

Derleme

Yağ asidi kompozisyon değişikliklerinin kalp damar hastalıkları açısından önemi

The importance of fatty acid composition changes in terms of cardiovascular diseases

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Öz

Bu derlemede ilk olarak; yağ asitlerinin yapısı, adlandırması, sınıflandırması ve fizyolojik etkileri gibi bilgiler verilmiş, sonrasında yağ asitleri ile kalp-damar hastalıkları arasındaki ilişkiyi araştıran çalışmalar irdelenmiştir. Yağ asitleri, yağların ve hücre zarının yapısına katılan, vücut için enerji kaynağı görevi üstlenmelerinin yanı sıra birçok metabolik yolakta yer alan, önemli fizyolojik işlevlere sahip biyolojik bileşiklerdir. Bu bileşikler diyetle alınabildiği gibi bir kısmı da vücutta öncül maddelerden sentezlenebilmektedir. Kültür, din, coğrafya, iklim gibi faktörlere göre besin tüketim şeklinin değişkenlik göstermesi ve yağ asidi metabolizmalarında görev alan enzimlerin aktiviteleri yağ asidi kompozisyonunu etkilemektedir. Yağ asitlerinin biyolojik etkileri, yağ asidi türüne göre farklılık gösterir. Bu nedenle, yağ asidi profilindeki değişiklikler, sağlık-hastalık durumu için değerli hale gelmekte ve yağ asidi kompozisyonu ile hastalıklar arasında ilişki kurulmaktadır. Bu kompozisyonun belirlenmesinde yağ dokusu, eritrosit hücre zarı, plazma ve serum gibi biyolojik örnekler kullanılmaktadır. Yağ asidi ölçüm işlemleri genellikle gaz kromatografisi yöntemiyle gerçekleştirilir. Ölçülen değerler kullanılarak oluşturulan indekslerle yağ asidi metabolizmasında görev alan enzimlerin aktiviteleri hesaplanır. Mevcut veriler, yağ asidi kompozisyonundaki değişikliklerin, özellikle kalp damar hastalıkları olmak üzere birçok kronik hastalık patolojisi ile ilişkili olduğunu ve biyobelirteç olarak kullanılma potansiyeli taşıdığını işaret etmektedir. Ancak, bu ilişki tam olarak aydınlatılamamıştır. Bu nedenle, güncel teknolojik yöntemlerden faydalanılarak özellikle tüm yağ asidi profilinin araştırıldığı yeni çalışmalar önemini korumaktadır.

Anahtar kelimeler: yağ asitleri; kalp-damar hastalıkları; biyobelirteç

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Recevied: 12.02.2020 accepted: 22.02.2020
Doi: 10.18663/tjcl.687043

Volume 11 Number 4 p: 323-333

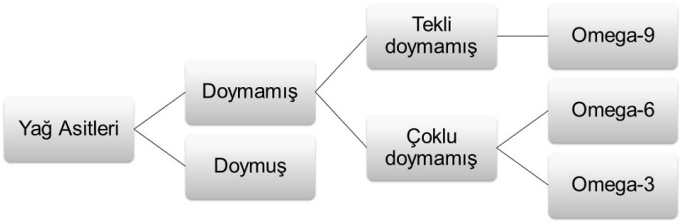
Abstract

In this review, information such as the structure, nomenclature, classification and physiological effects of fatty acids have been given initially, and then studies investigating the association between fatty acids and cardiovascular diseases have been examined. Fatty acids that are involved in the structure of lipids and cell membranes and take part in many metabolic pathways as well as being an energy source for the body are biological compounds that have important physiological activities. These compounds can be taken by diet or some of them can be synthesized from the precursors in the body. Enzyme activities involved in fatty acid metabolism and variation of food consumption according to factors such as culture, religion, geography and climate affect the fatty acid profile. The biological activities of fatty acids differ according to the type of fatty acids. For this reason, changes in the fatty acid profile become important for the health-disease situation and the association between fatty acid composition and the diseases is established. Biological samples such as adipose tissue, erythrocyte cell membrane, plasma and serum are used in order to determine this composition. Fatty acid measurement processes are generally carried out by gas chromatography. The activities of enzymes involved in fatty acid metabolism can be estimated by the indexes obtained from the measured values. Current data indicate that changes in the fatty acid composition are associated with many diseases, especially cardiovascular diseases, and have the potential to be used as biomarkers. However, this association has not been fully clarified. Therefore, new studies that research especially the entire fatty acid profile by taking advantage of current technological methods remain important.

Keywords: fatty acids; cardiovascular diseases; biomarkers

Yağ Asitlerinin Yapısı, Adlandırmaları ve Sınıflandırmaları

Yağ asitleri, triaçilgliseroller (trigliseritler), fosfolipitler ve diğer karmaşık yağların ana bileşenleri olan alifatik zincire sahip tek karboksil grubu içeren asitlerdir [1]. İçerdikleri karbon adedi, doymamış bağ sayısı ve bu bağ(lar)ın konumuna göre sınıflandırılmaktadır. Memelilerde bulunan yağ asitleri 12-24 karbon uzunluğuna ve 0-6 çift bağa sahip olabilmekle birlikte 14 karbondan kısa ve 22 karbondan uzun yağ asitlerinin miktarı çok düşüktür [2]. Yağ asitleri yapılarında bulunan karbon sayısına göre kısa (C2-4), orta (C6-10), uzun (C12-20) ve çok uzun zincirli (C>22); çift bağ içerip içermemelerine göre ise doymamış ve doymuş (Şekil 1) yağ asitleri olarak sınıflandırılmaktadır [3, 4]. Yapısında çift bağ içeren yağ asitleri; aralarında çift bağ bulunan karbonlara ait hidrojen atomları aynı tarafta ise "cis" ters tarafta ise "trans" olarak adlandırılmaktadır. Ayrıca, doymamış yağ asitleri çift bağ(lar)ın sayısı ve konumuna göre tekli doymamış ve çoklu doymamış (Şekil 1) yağ asitleri olarak gruplandırılmaktadır [5].



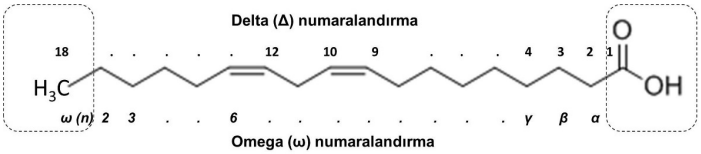
Şekil 1: Yağ asitlerinin doymamışlık derecesine göre sınıflandırması

Yağ asitlerinin sistematik adlandırmalarının yanı sıra özel adları da vardır, örneğin; 9,12-oktadekadienoik asidin özel adı linoleik asit (LA)'tir. Aynı zamanda, şematik bir formül olarak da kısaltılabilirler. Bu kısaltmalar yağ asidindeki karbon atomu sayısı, çift bağ sayısı ve çift bağların konumuna göre belirlenir (Tablo 1). Omega (ω) numaralandırma sisteminde karboksil grubu bulunan karbon 1. karbon olarak numaralandırılır. Karboksil karbonunun yanındaki (ikinci) karbon atomu α, üçüncü karbon atomu β, dördüncü karbon atomu γ ve terminal metil grubundaki karbon atomu ise zincir uzunluğundan bağımsız olarak ω (omega) veya n şeklinde adlandırılır (Şekil 2). Bu sistemde çift bağın konumu omega ucuna göre

Tablo 1: Bazı yağ asitlerinin adlandırma ve numaralandırmaları

Yaygın ad	Sistematik ad	Delta numaralandırma	Omega numaralandırma
Laurik asit	Dodekanoik asit	12:00	12:00
Miristik asit	Tetradekenoik asit	14:00	14:00
Palmitik asit	Hekzadekanoik asit	16:00	16:00
Palmitoleik asit	9–Hekzadekenoik asit	16:1 Δ9	16:1 n–7
Stearik asit	Oktadekanoik asit	18:00	18:00
Oleik asit	cis–9–Oktadekenoik asit	18:1 Δ9	18:1–cis n–9
Elaidik asit	trans–9–Oktadekenoik asit	18:1 Δ9	18:1–trans n–9
Linoleik asit	all cis–9,12–Oktadekadienoik asit	18:2 Δ9,12	18:2–cis n–6
Linoelaidik asit	all trans–9,12–Oktadekadienoik asit	18:2 Δ9,12	18:2–trans n–6
α–Linolenik asit	all cis–9,12,15–Oktadekatrienoik asit	18:3 Δ9,12,15	18:3 n–3
γ–Linolenik asit	all cis–6,9,12–Oktadekatrienoik asit	18:3 Δ6,9,12	18:3 n–6
Arasidik asit	Eikozanoik asit	20:00	20:00
Dihomogamalinolenik asit	all cis–8,11,14–Eikozatrienoik asit	20:3 Δ8,11,14	20:3 n–6
Arasidonik asit	all cis–5,8,11,14–Eikozatetraenoik asit	20:4 Δ5,8,11,14	20:4 n–6
Eikozapentaenoik asit	all cis –5,8,11,14,17–Eikozapentaenoik asit	20:5 Δ5,8,11,14,17	20:5 n–3
Behenik asit	Dokosanoik asit	22:00	22:00
Erusik asit	cis–13–Dokosenoik asit	22:1 Δ13	22:1 n–9
Dokozahekzaenoik asit	all cis 4,7,10,13,16,19–Dokozahekzaenoik asit	22:6 Δ4,7,10,13,16,19	22:6 n–3
Lignoserik asit	Tetracosanoik asit	24:00:00	24:00:00
Nervonik asit	cis–15–Tetrakosenoik asit	24:1 Δ15	24:1 n–9

belirtilir ve sadece birinci karbonun yeri ifade edilir. Örneğin LA, omega karbonuna en yakın çift bağ altıncı karbondan başladığı için 18:2 ω–6 veya 18:2 n–6 olarak gösterilir. Delta (Δ) numaralandırma sisteminde ilk karbon karboksil grubu bulunan karbon atomu olup numaralandırma metil grubuna doğru artarak devam eder, doymamış bağın konumu ilk karbona göre belirtilir. On sekiz karbon atomuna sahip, 9 ile 10. ve 12 ile 13. karbon atomları arasında iki çift bağ bulunan LA delta (Δ) sistemine göre 18:2 Δ9,12 şeklinde gösterilir [6].



Sistematik adlandırma	9,12-oktadekadienoik asit
Özel adı	Linoleik asit
Delta (Δ) sistemi	18:2 $\Delta^{9,12}$
Omega (ω) sistemi	18:2 n-6

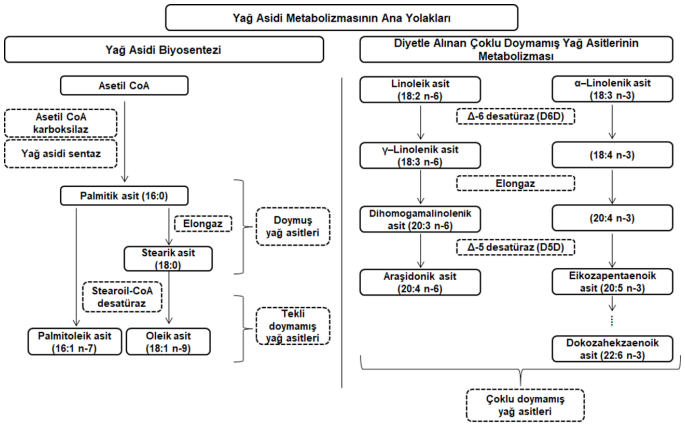
Şekil 2: Yağ asitlerinin yapısı ve adlandırmaları

Yağ Asitlerinin Kaynağı, Vücutta Sentezleri ve Metabolizmaları

Yağ asitleri, trigliseritlerin ve dolayısıyla diyetle alınan yağların ana bileşenleridir. Besinlerin içerdiği yağ miktarı ve yapılarında barındırdıkları yağ asidi türü değişkenlik göstermekte; işleme, depolama ve pişirme yöntemlerinden etkilenebilmektedir [7, 8]. Dolayısıyla yağ asidi tüketim şekli; kültürel, dini, coğrafik uygulama farklılıklarının yanı sıra öğünden öğüne, günden güne, mevsimden mevsime de farklılık göstermektedir [9-13]. Sağlıklı insanlarda, diyetle alınan yağ asitlerinin çoğu sindirim ve emilimleri verimli bir şekilde gerçekleştikten sonra kan dolaşımına geçer [14]. Esansiyel olanlar dışındaki yağ asitleri insan vücudunda, glikoz gibi öncüllerden veya diğer yağ asitlerinden sentezlenebilirken, esansiyel yağ asitleri vücutta sentezlenemediği için diyetle alınması zorunludur [6]. Omega (veya n) 3 ve 6 pozisyonlarına çift bağ ekleyen enzimler insan vücudunda bulunmadığı için n-3 ve n-6 yağ asitleri vücutta sentezlenemezler. Esansiyel yağ asitlerinden olan LA; yeşil bitkiler, keten tohumu, fındık ve soya fasulyesi gibi bazı

bitkisel yağlardan elde edilen n-6 türevi çoklu doymamış bir yağ asidi olup, eikozanoid sentezinde görev alan araşidonik asit (AA)'in öncülüdür. Omega-3 türevi yağ asitleri olan EPA ve dokozahekzaenoik asit (DHA)'in vücutta, yine esansiyel bir yağ asidi olan ALA'dan sentezleri çok kısıtlı olarak gerçekleşmekle birlikte esas kaynakları diyetle alınan balık ürünleridir [15, 16].

Vücutta sentezlenebilen yağ asitlerinin öncül maddelerden sentezi karbonhidratlar, laktat veya amino asitler ile asetil-CoA kullanılarak esas olarak karaciğerde olmak üzere, yağ dokusunda, daha az miktarda kas dokusunda ve laktasyon süresince meme bezlerinde gerçekleşir. Bu yolağın son ürünü, insan vücudundaki yağ asitlerinin %20-30'u olan palmitik asittir (C16: 0) ve palmitik asit, çift bağ eklenerek (desatürasyon) ve/veya zincir uzatılarak (elongasyon) başka yağ asitlerine dönüştürülebilir [17]. Yağ asitlerinin doymamışlık derecesi, hücre zarı fosfolipitleri ve depolanmış trigliseritlerin fiziksel özelliklerini etkilediği için yağ asitlerindeki çift bağ sayısı ve bu süreçte yer alan enzimler fizyolojik açıdan önem arz etmektedir. İnsanda yağ asitlerinin doymamış hale getirilmesinde stearoil-CoA (Δ-9) desatüraz (SCD), Δ-6 desatüraz (D6D) ve Δ-5 desatüraz (D5D) enzimleri görev almaktadır [18]. SCD, özellikle stearoil-CoA ve palmitoleil-CoA'dan oleat ve palmitoleat sentezi olmak üzere doymuş yağ asitlerinden tekli doymamış yağ asitlerinin biyosentezini katalize eden ve hız kısıtlayıcı basamak olan bir endoplazmik retikulum (ER) enzimidir [19]. Bu enzim NAD(P)H, flavoprotein sitokrom B5 redüktaz ve elektron alıcı sitokrom B5 ile moleküler oksijenin kullanıldığı elektron aktarımını kataliz ederek doymuş yağ asidinin yapısına Δ (delta)-9 konumundan bir çift bağ ekleyerek tekli doymamış yağ asidi meydana getirir [20]. D6D ve D5D esas olarak, fosfolipitlere esterleşen ve hücre zarının akışkanlığının korunmasına katkıda bulunan çoklu doymamış yağ asitlerinin sentezinde görev alan; LA (18:2 n-6) ve α-linolenik asidin (ALA) (18:3 n-3) uzun zincirli metabolitleri olan AA (20:4 n-6) ve eikozapentaenoik aside (EPA) (20:5 n-3) dönüşümünü sağlayan (Şekil 3) enzimlerdir [21, 22]. D6D omega-6 serisinde 18:2'nin 18:3'e ve omega-3 serisinde 18:3'ün 18:4'e dönüşümünü sağlarken, D5D ise dihomo-γ-linolenik asidin (DGLA) AA'ya dönüşümünü hız sınırlayıcı olarak katalize eder [22]. İnsan vücudundaki desatüraz enzim aktivitelerinin doğrudan ölçülmesi kolay değildir, ancak sentezlenen ürünlerin kullanılan öncül maddelere oranıyla enzim aktivitelerinin hesaplanması mümkündür. Satürasyon indeksleri olarak da adlandırılan bu hesaplamalar; SCD için [palmitoleik asit / palmitik asit veya oleik asit (OA) / stearik asit (SA)], D5D için [AA / DGLA], D6D için ise [gama-linolenik asit (GLA) / LA] formülleriyle yapılabilmektedir [23, 24]. Yağ asitlerinin fizyolojik rolleri ve desatüraz enzimlerinin yağ asidi profilini doğrudan etkilemeleri nedeniyle satüraz indekslerinin hastalık süreçleriyle ilişkili olup olmadığı araştırmalara konu olmuştur [25, 26].



Şekil 3: Yağ asidi metabolizmasının ana yolakları

Yağ Asitlerinin Fizyolojik Rolleri

Yağ asitleri kanda, daha karmaşık yağların (trigliseritler, fosfolipitler, kolestrol esterleri gibi) bileşeni halinde lipoproteinlerin yapısına katılarak taşınır, ancak bazı esterleşmemiş yağ asitleri serbest yağ asidi (SYA) olarak dolaşımda bulunur [27]. Birçok metabolik yolakta görev alan yağ asitleri fizyolojik olaylar için büyük öneme sahiptir. Oksidasyonları sonucu yüksek enerji ortaya çıkması nedeniyle temel enerji kaynağı olarak işlev görürler [28, 29]. Beyin hariç çoğu aerobik doku tarafından glikoza alternatif bir enerji kaynağı olarak kullanılabilmeleri nedeniyle açlık gibi sınırlı glikoz mevcudiyeti durumlarında değerli hale gelirler [28, 29]. Yağ asitleri, hücre zarı fosfolipitlerinin bileşenleridir ve farklı hücreler farklı yağ asidi bileşimine sahiptir. Bunlar diyet, metabolizma, hormonal çevre ve genetik gibi faktörlerden etkilenebilir [30, 31]. Hücre zarının yağ asidi profili, zarın fiziksel yapısını, dolayısıyla da zar proteinlerinin (reseptörler, enzimler, iyon kanalları vb.) hareket ve işlevlerini etkiler [30, 31]. Ayrıca, hücre zarı yağları diaçilgliserol, seramit, lizofosfolipit ve endokannabinoidler gibi hücre haberleşmesinde yer alan moleküllerin öncülleridir. Bu sinyal moleküllerinin yağ asidi bileşimleri ve biyolojik aktiviteleri kaynak aldıkları hücre zarının yağ asidi bileşiminden etkilenmektedir [32, 33]. Hücre zarı yağlarından salınan veya hücrelere alınan yağ asidi türü metabolik, işlevsel veya sinyal ile ilgili yolaklar üzerinde önemli rollere sahip olabilir. Örneğin, doymuş yağ asitlerinden miristik

asit (14: 0) ve palmitik asit (16: 0), hücre zar proteinlerinin açılasyonu ve böylece zara tutunmalarında görev alırken [34, 35], ω-6 çoklu doymamış yağ asidi olan AA, pek çok düzenleyici rolü olan prostaglandin (PG)'ler, tromboksanlar ve lökotrien (LT)'ler gibi eikozanoidlerin sentezinde kullanılan öncül moleküldür [18, 36]. Bazı yağ asitleri, transkripsiyon faktörlerinin ekspresyon veya aktivitesini düzenleyebilir, böylece hücrelerin gen ekspresyonu ve protein üretimi üzerinde etkiye sahip olabilirler [37]. Bu etkiler, yağ asitlerinin yağ asidi sentezi ve oksidasyonu, lipoprotein metabolizması, insülin duyarlılığı ve inflamasyon gibi metabolik olayların düzenlemesinde rol üstlenmesine olanak sağlar [37]. Bu nedenle yağ asitlerinin hücre/doku metabolizması ve fonksiyonu, hormonal ve diğer sinyallere yanıt verme gibi hayati işlevler üzerinde etkili olabilecek bir biyolojik aktiviteye sahip olduğunu, böylelikle sağlık ve hastalık riskini etkilediğini söylemek mümkündür.

Yağ Asitleri ve Hastalıklar Arasındaki İlişki

Yağ asitlerinin fizyolojik rollerinden dolayı hastalıkların gelişim ve tedavi süreçlerinde etkili olabileceği hipotezi birçok çalışmaya konu olmuş; adipoz doku, eritrosit hücre zarı ve plazma gibi biyolojik örnekler üzerinde araştırmalar yapılmıştır. İncelemelerde kullanılan biyolojik materyalin türü, yağ asidi kompozisyonuna dair elde edilecek verilerin hangi zaman aralığını yansıtacağını etkilemektedir. Örneğin; serum ve plazma örnekleri güncel yağ asidi kompozisyonunu gösterirken, eritrosit hücre zarı eritrosit ömrüne benzer şekilde birkaç aylık, adipoz doku ise yıllarla ifade edilen sürelere dair bilgi sağlamaktadır [38, 39]. Psikiyatrik hastalıklar, kanser, inflamatuvar hastalıklar, insülin direnci ve nörodejeneratif hastalıklar yağ asitleri ile ilişkileri bakımından araştırılan hastalıklardan bazıları [40-45] olmakla birlikte kalp-damar hastalıkları (KDH), yağ asitleri ile ilişkisi bakımından incelenen hastalıkların başında gelmektedir [46].

Psikopatoloji ile yağ asitleri arasındaki ilişkinin incelendiği bir çalışmada, eritrosit hücre zarı yağ asidi kompozisyonu araştırılmıştır. Ortaya çıkan sonuçlar şizofreninin negatif semptomları ile miristik asit, margarik asit ve nervonik asit arasında negatif; eikosinoik asit, erüsik asit, GLA ve dokosadienoik asit arasında pozitif korelasyon bulunduğu yönündedir [43]. Diyetle alınan yağ asidi ile kolorektal kanser arasında ilişki bulunabileceği hipoteziyle tasarlanan bir çalışmada, adipoz doku yağ asidi profili gaz kromatografisi yöntemiyle analiz edilmiş, kolerektal kanser hastalarında bazı yağ asidi (palmitoleik asit [16:1n–9], DGLA [20:3n–6] ve dokosapentaenoik asit (DPA) [22:5n–3]) düzeylerinin kontrol grubuna göre yüksek, ALA düzeyinin ise düşük olduğu bulunmuştur. Ayrıca kolorektal kanser hastalığı bulunanların çoklu doymamış yağ asidi düzeylerinin arttığı tespit edilmiştir. Bununla birlikte yağ asidi profilindeki bu değişikliklerin diyet kaynaklı mı yoksa metabolizma değişikliği neticesinde mi meydana geldiğinin araştırılması gerektiği vurgulanmıştır [44]. Serum yağ asitlerinin ülseratif kolitle ilişkili olup olmadığını inceleyen bir araştırmada; ülseratif kolit olgularında doymuş yağ asidi ve AA düzeyinde azalma, OA, LA, EPA ve DPA düzeyinde artış tespit edilmiş, serum yağ asidi düzeylerinin sitokin üretimini değiştirerek immünomodülatör etki gösterebileceği ileri sürülmüştür [47]. HIV ile enfekte hastaların plazma örneklerinde yapılan bir çalışmada düşük GLA seviyesi, düşük CD4 hücre sayısı ve artmış ölüm veya hastaneye yatış riski ile ilişkili bulunmuş ve yağ asitlerinin tedavide olumlu katkılar sağlayabileceği ifade edilmiştir [42]. Alkole bağlı olmayan yağlı karaciğer hastalığının yağ asidi metabolizma bozuklukları ile birlikte görülmesinden hareketle, yağ asitlerinin biyobelirteç olma potansiyeli bulunduğunu düşünen araştırmacılar, alkolik olmayan yağlı karaciğer hastalığı bulunanların eritrosit yağ asidi profilini incelemiştir. Elde edilen veriler alkolik olmayan yağlı karaciğer hastalığında palmitik asit, palmitoleik asit, SA ve OA'nın azaldığı; özellikle EPA ve DHA olmak üzere çoklu doymamış yağ asitlerinin arttığı yönünde olup yağ asitlerinin biyobelirteç olarak kullanılabilmesi için ileri araştırmaların gerekliliği vurgulanmıştır [48]. Tüketilen yağın insülin direnci üzerinde etkisi olup olmadığını sorgulayan bir araştırmada sağlıklı gönüllüler doymuş yağ asidi ve tekli doymamış yağ asidi içerikli diyet grupları olmak üzere ikiye ayrılmış ve üç ay boyunca bu diyetler uygulanmıştır. Ortaya çıkan sonuçlar; doymuş yağ asidi diyeti tüketiminin insülin duyarlılığında azalmaya neden olduğunu, tekli doymamış yağ asidi diyeti uygulanan grupta ise insülin duyarlılığında bir değişiklik meydana getirmediğini göstermiştir [49]. Yağ asitlerinin Alzheimer Hastalığı ile ilişkisini araştıran bir çalışmada, eritrosit yağ asidi profili, pozitron emisyon tomografisi (PET) ile ölçülen neokortikal beta-amiloid yükü sonuçlarıyla karşılaştırılmıştır. Klinik öncesi fazdaki (bilişsel bozulmadan önce) değişikliklerin incelendiği bu çalışmada yüksek neokortikal beta-amiloid yük tespit edilen hastalarda artmış AA ve azalmış DPA profili gözlenmiştir [50].

Yağ Asitleri ve Kalp-Damar Hastalıkları Arasındaki İlişki

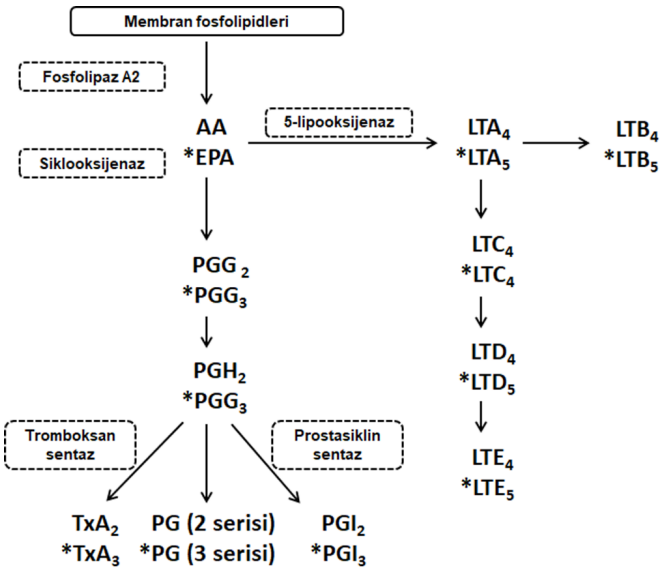
KDH tüm dünyada insidansı, prevelansı ve mortalitesi yüksek olan hastalıkların başında gelmektedir [51, 52]. Bu hastalıkların tanı, tedavi ve yönetiminde kullanılabilecek yeni yaklaşımların araştırılması büyük öneme sahiptir. Yağ asitlerinin KDH ile ilişkili olabileceği uzun yıllardır araştırmalara konu olmaktadır. Yağ asitlerinin ventriküler fibrilasyon ile ilişkisinin izole sıçan kalbinde araştırıldığı bir çalışmada palmitik asidin miyositlerde kalsiyum akışını artırarak ventriküler fibrilasyon oluşturduğu bulunmuştur [53]. Grekin vd. sıçanlar üzerinde yağ asidinin sempatik etkilerini incelemiş; portal vene sodyum oleat infüzyonunun sempatik aktivasyonla adrenalin, noradrenalin seviyelerini ve kan basıncını artırdığını göstermişlerdir [54]. Kobay ventrikül miyositlerinde voltaj-kenetleme yöntemi ile yağ asitlerinin voltaj duyarlı kalsiyum akışı üzerindeki etkileri incelenmiş; yağ asitlerinin kalsiyum akışını artırarak aritmi oluşturabileceği gösterilmiştir. Ancak, 12 karbondan daha kısa zincirli veya esterleşmiş (oleik ve palmitik metil esterler) yağ asitlerinde böyle bir etki görülmemiştir. Aritmik etkinin uzun zincirli ve serbest (esterleşmemiş) karboksil grubu olan yağ asitleri tarafından oluşturulabileceği ortaya konmuştur [55]. Yağ asitlerinin KDH ile ilişkisi birçok klinik çalışma ile de irdelenmiştir. Yağ asidi ile ailesel KDH riski arasındaki ilişkinin araştırıldığı bir çalışmada bireylerin serum serbest yağ asidi (SYA) düzeyinin yüksekliği ile ebeveynlerin KDH riski arasında doğrusal bir orantı olduğu gösterilmiştir [56]. Koroner arter hastalığı (KAH) teşhisinde SYA tolerans testinin kullanılma potansiyelini araştıran bir çalışmada, katılımcılara yağ içerikli solüsyon uygulanmış ve heparinle lipoliz indüklenerek SYA düzeyinde artış sağlanmıştır. Serum SYA düzeyinde meydana gelen artış ve ilerleyen süredeki düzeyleri KAH bulunanlarda KAH bulunmayanlara göre daha yüksek bulunmuş, SYA'nın KAH için erken indikatör olarak kullanılma potansiyeline işaret edilmiştir [57]. Yağ asitlerinin akut proinflamatuvar etkisini incelemeyi hedefleyen bir araştırmada, sağlıklı gönüllülere yağ ve heparin uygulaması yapılarak kan SYA düzeylerinde artış sağlanmış, bu artışın oksidatif stresi indüklediği, proinflamatuvar etki gösterdiği ve brakial arterde vazodilatasyonu bozduğu bulunmuştur [58]. Obez ve zayıf kadınlar üzerinde yapılan klinik bir çalışmada, zayıf kadınlara artan konsantrasyonlarda SYA içerikli intravenöz infüzyon ve obez kadınlara serum SYA seviyesini düşürmek için antilipolitik etkili nikotinik asit analoğu (acipimox) uygulamaları yapılmıştır. Zayıf kadınlarda SYA yükselmesinin mikrovasküler fonksiyonu bozduğu ve obez kadınlarda SYA azalmasının mikrovasküler fonksiyonu iyileştirdiği görülmüştür [59]. Mathew vd. kan yağ asidi konsantrasyonundaki artışın ateroskleroz ve diğer KDH'ye neden olan erken vasküler anormallikleri başlatabileceğine dair veriler elde etmiştir [60]. Artriyal fibrilasyon ile yağ asidi ilişkisinin incelendiği bir araştırmada, 65 yaşından büyük kadın ve erkeklerden oluşan katılımcılarda SYA düzeyinin yüksek olmasının atrial fibrilasyona neden olduğu bulunmuştur [61].

Farklı yağ asitlerinin biyolojik aktivitelerinin de farklı olması nedeniyle, KDH'de toplam yağ asidi düzeyi değişikliklerinin incelenmesinden öte kompozisyon değişikliklerinin analiz edilmesiyle daha detaylı veriler elde edilmektedir. Her bir yağ asidi için gözlenen değişiklik doğrudan incelenebileceği gibi, kompozisyon verileri kullanılarak yağ asidi metabolizmasında görev alan enzimlerin aktiviteleri, dolayısıyla da yağ asidi metabolizması hakkında da bilgi sağlanabilmektedir [62, 63]. Bunun için enzimlerin ürünü olan yağ asidinin, substrat olan yağ asidine oranından faydalanılmaktadır. Cis-palmitoleik asit sentezinde görev alan SCD enzimi aktivitesinin kalp yetmezliği ile bağlantılı olup olmadığını konu alan bir çalışmada katılımcıların plazma yağ asidi kompozisyonu gaz kromatografisi ile belirlenmiş, 16:1n-7/16:0 ve 18:1n-9/18:0 oranları kullanılarak SCD aktivitesi hesaplanmıştır. Çalışma verileri cis-palmitoleik asit ve SCD aktivitesi ile kalp yetmezliği arasında pozitif bir korelasyon bulunduğunu göstermiştir [62]. KDH kaynaklı ölüm riski ile desatüraz enzim aktiviteleri arasında korelasyon bulunup bulunmadığının inceleyen bir çalışmada, gaz kromatografisi ile ölçülen plazma ve eritrosit hücre zarı yağ asitleri üzerinden desatüraz enzim aktiviteleri (SCD: 16:1n-7/16:0, D6D: 18:3n-6/18:2, D5D: 20:4n-6/20:3) hesaplanmıştır. KDH mortalitesi ile SCD aktivitesi arasında pozitif, D5D aktivitesi arasında negatif korelasyon tespit edilmiş; D6D aktivitesi arasında ise anlamlı bir korelasyon saptanamamıştır [63].

Yağ asidi kompozisyonunun yorumlanmasında kullanılan bir yöntem de yağ asitlerinin benzer özelliklerine (doymuş, çoklu doymamış, omega 3, omega 6 gibi) göre gruplandırılması ve çeşitli indeksler oluşturulmasıdır. Örneğin Omega 3 indeksi, eritrosit hücre zarındaki ω-3 türevi yağ asitlerinin (EPA ve DHA) yüzdelerinin toplamı olarak tanımlanır ve KDH açısından bu değerin %8'den büyük olması düşük risk %4'ten küçük olması yüksek risk olarak değerlendirilir [64].

Omega-3 türü yağ asitleri KDH'ye karşı koruyucu olarak bilinmekle birlikte etki mekanizmaları tümüyle açıklanmış

değildir [65]. Yağ asitleri, yapılarında bulunan çift bağ sayısı ve bu bağların konumuna göre kalp-damar sistemi üzerinde farklı etkiler ortaya çıkarmaktadır [66]. Omega-3 yağ asitleri içerdikleri çift bağ sayısının fazla olması ve yapılarında uzun karbon zinciri içermeleri nedeniyle hücre zarı akışkanlığını etkileyerek hücre zarı proteinleri (reseptörler, enzimler, iyon kanalları vb.), yağları ve sinyal moleküllerinin aktivitelerini değiştirebilmektedir [67]. Bu yağ asitlerinin; antiinflamatuvar özellikleriyle [68], sinyal yolaklarını etkileyerek [69] ve antiaritmik [70] aktiviteleriyle kalp-damar sistemi için koruyucu etki yaptıkları gösterilmiştir. Omega-3 yağ asitleri 3-dihidroksi-3-metilglutaril-CoA enzimini baskılayarak kolesterol seviyesini düşürmekte böylece de anti-arterosklerotik etki göstermektedir [71]. Kardiyoprotektif etkinin oluşumunda ω-3 türevi yağ asitlerinin eikozanoid sentezinde öncül olarak kullanılması da önemli bir etkendir. Eikozanoidler, esansiyel yağ asitlerinden türetilen 20 karbonlu çoklu doymamış yağ asitlerinin (örn; DHGL, AA ve EPA) oksidasyon ürünleridir. Fosfolipaz A2 enzimi hücre zarı yağlarından yağ asitlerini ayırdıktan sonra; siklooksijenazların etkisiyle PG'ler, lipooksijenazların etkisiyle LT'ler oluşturulur (Şekil 4). Öncül bileşik olarak ω-6 türevi yağ asidi olan AA kullanılması durumunda 2 çift bağ içeren ve kalp-damar sağlığı açısından olumsuz etkilere sahip "2" serisi PG'ler, tromboksan A2 (TxA2) ve prostasiklin I2 (PGI2) meydana gelirken, ω-3 türevi EPA kullanıldığında "3" serisi PG'ler, tromboksan A3 (TxA3) ve prostasiklin I3 (PGI3) oluşmaktadır [71, 72]. Benzer şekilde lipooksijenaz yolağında; AA'dan "4" serisi LT'ler oluşurken EPA'dan "5" serisi LT'ler meydana gelmektedir [71]. İnsanlarda doku fosfolipidinin AA içeriği daha yüksek olduğu için AA'dan üretilen eikozanoidler diğerlerine (DHGL ve EPA'dan üretilen) göre daha baskındır [73]. PG'ler mide salgısı, rahim kasılması, üreme, kan basıncı kontrolü ve inflamasyon gibi çok çeşitli süreçleri düzenlemektedirler [74]. TxA2 platelet agregasyonu ve vazokonstrüksiyona neden olurken TxA3'ün bu etkileri daha zayıftır [75]. PGI2 ve PGI3'ün fizyolojik etkileri ise platelet agregasyonunun inhibisyonu ve vazodilatasyon şeklindedir. Özetlemek gerekirse; eikozanoidler, sentezlerinde yer alan öncül yağ asidi türüne göre farklı fizyolojik etkiler oluşturmaktadırlar. Omega-3 yağ asitlerinden sentezlenen eikozanoidler ω-6 türevinden sentezlenenlere kıyasla, platelet agrege etme, vazokonstrüksiyon oluşturma ve inflamatuvar etkilerinin daha düşük olması gibi nedenlerle kalp-damar sistemi üzerinde koruyucu özellik göstermektedirler [76].



Şekil 4: Araşidonik asit ve eikozapentaenoik asitten eikozanoid sentezi

AA: araşidonik asit, EPA: eikozapentaenoik asit, PG: prostaglandin, LT: lokotrien TxA: tromboksan

Epidemiyolojik çalışmalar, Grönland'da yaşayan ve geleneksel diyetleri yüksek miktarda balık içeren Eskimo toplumunda, ateroskleroz ve kronik inflamatuar hastalık insidansının düşük olduğunu göstermiştir [77]. Bu toplumda, plazma trigliserit, düşük yoğunluklu lipoprotein (LDL) ve toplam kolesterol düzeyleri düşük, yüksek yoğunluklu lipoprotein (HDL) düzeyleri yüksektir [78]. Bu farklılıklar, EPA ve DHA bakımından zengin içeriğe sahip olmasından dolayı balık tüketimine atfedilmiş olup, başka toplumlarda da deniz ürünleri tüketimi düşük koroner kalp hastalığı ve inflamatuvar hastalık riski ile ilişkilendirilmiştir [78, 79]. Deniz ürünlerinden alınan EPA, trombositler ve endotelyal hücreler dahil olmak üzere hücre zarlarının fosfolipitlerine dahil edilir. Tromboksan sentezinde AA yerine EPA kullanıldığında TxA2'ye göre zayıf platelet agregasyonu ve vazokonstrüksiyon gösteren TxA3, agregasyon inhibisyon gücü PGI2'ye yakın olan PGI3 oluşmaktadır [80]. Ayrıca hem EPA hem de DHA'nın, D6D için LA ile yarışarak AA sentezini, böylece de eikozanoid oluşumu için kullanılabilirliğini azalttığı öne sürülmüştür [81]. Öte yandan bu yağ asitleri, AA'dan türetilen LT'lerin (4 serisi) oluşumunu azaltarak daha zayıf inflamatuvar etkili LT'lerin (5 serisi) oluşumunu artırabilir [80]. Bu nedenlerle, ω-3 yağ asitleri ateroskleroz gelişimine ve diğer kalp damar hastalıklarına karşı koruma sağlayabilir.

Sonuç olarak, yağ asitlerinin çeşitli biyolojik aktivitelerinden dolayı birçok fizyolojik süreçte önemli rol üstlendiklerini söylemek mümkündür. Biyolojik aktivitelerinin ise yağ

asidi türüne göre değişkenlik göstermesi nedeniyle yağ asidi kompozisyon değişiklikleri ile hastalıklar arasında ilişki olabileceği çok sayıda çalışmaya konu olmuş ve güncelliğini korumaktadır. Bu hastalıkların başında ise KDH gelmektedir. KDH-yağ asidi kompozisyonu ilişkisi tam olarak aydınlatılmamış olmasına rağmen, mevcut veriler genel olarak yağ asidi kompozisyonunun KDH ile ilişkili olabileceğini işaret etmektedir [45, 46, 61, 82-84]. Meta analiz verileri de yağ asitlerinin KDH için biyobelirteç olarak kullanılabileceğini tartışmakla birlikte var olan bilginin eksik olduğunu ve klinik çalışmalarla güçlendirilmesi gerektiğini vurgulamaktadır [85, 86]. Dahası besin tüketimi, yaşam tarzı, genetik havuz gibi toplumsal farklılıkların yağ asidi kompozisyonunda değişiklikler meydana getirebileceği [9-13] dikkate alınırsa farklı toplumlarda yapılacak çalışmalar KDH-yağ asitleri ilişkisinin aydınlatılmasına kayda değer katkılar sağlayacaktır [87]. Ayrıca gelişen teknolojinin daha detaylı analiz imkanları sunması bu konudaki güncel çalışmalarla yeni bilgiler keşfedilmesini olanaklı hale getirmektedir.

Maddi Destek ve Çıkar İlişkisi

Bu yayın için herhangi bir maddi destek alınmamıştır.Yazarların herhangi bir çıkar dayalı ilişkisi yoktur.

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To cite this article: Tuna AT, Kocayiğit H, Şahin F, Gök K. İntraoperatif kardiyomyopati gelişen plasenta perkreta olgusunda perioperatif anemi yönetimi. Turk J Clin Lab 2020; 4: 334-337.

Olgu Sunumu

İntraoperatif kardiyomyopati gelişen plasenta perkreta olgusunda perioperatif anemi yönetimi

Management of perioperative anemia in a case of placenta percreata who had intraoperative cardiomyopathy

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Öz

Elektif cerrrahi planmalasında hastada bulunan demir eksikliği anemisinin preoperatif tedavi edilmesi morbidite ve mortalitede azalma ile ilişkili bulunmuştur. Oral demir tedavisinin yetersiz kaldığı ya da operasyon öncesi sürenin kısıtlı olduğu durumlarda İV demir tedavisi uygulanmalıdır. Gebelerde preoperatif dönemde klinik semptomu olmasa bile intraoperatif ya da postoperatif dönemde peripartum kardiyomyopati (PPKMP) gelişebileceği her zaman akılda bulundurulmalıdır.Bu olgu sunumuyla plasental invazyon anomalisi bulunan, sezaryen operasyonu sırasında ani KMP gelişen, peroperatif anemi tedavisi için intravenöz demir tedavisi uyguladığımız gebe hastayı güncel literatür ışığında tartışmayı amaçladık.

Anahtar Kelimeler: peripartum kardiyomyopati; plasenta perkreta; anemi

Abstract

Preoperative treatment of iron deficiency anemia was associated with a decrease in morbidity and mortality. IV iron therapy should be used in cases where oral iron therapy is insufficient or the time before operation is limited. It should always be kept in mind that pregnant women can develop peripartum cardiomyopathy (PPCMP) in the intraoperative or postoperative period, even if they do not have clinical symptoms in the preoperative period. With this case report, we aimed to discuss the pregnant patient who has placental invasion anomaly, who developed sudden CMP during cesarean operation, and we applied intravenous iron therapy for the treatment of peroperative anemia in the light of current literature.

Keywords: peripartum cardiomyopathy; placenta percreata; anemia

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Volume 11 Number 4 p: 334-337

Giriş

Anemi en ciddi küresel halk sağlığı sorunlarından biridir ve Dünya Sağlık Örgütü anemiyi hemoglobin (Hb) konsantrasyonunun gebeliğin herhangi bir döneminde 110 g/L'nin altında olması olarak tanımlamaktadır. Gebelerde anemi insidansı yaklaşık olarak %38'dir. Gebelerde aneminin en sık nedeni demir eksikliği anemisi (DEA) olarak bilinmektedir ve düşük doğum ağırlığına bağlı fetal mortalite ve neonatal morbidite risk artışına neden olabilmektedir [1].

Peripartum kardiyomyopati (PPKMP) belirgin bir neden olmaksızın gebeliğin son trimesterinde ya da postpartum 6 ay içerisinde gelişen akut kalp yetmezliği olarak tanımlanır PPKMP ciddi pulmoner konjesyon ve/veya tromboembolik olaylara yol açabilir ve artmış mortalite (% 30-60) ile ilişkilidir [2]. Bu olgu sunumuyla plasental invazyon anomalisi bulunan, sezaryen operasyonu sırasında ani KMP gelişen, peroperatif anemi tedavisi için intravenöz (İV) demir tedavisi uyguladığımız gebe hastayı güncel literatür ışığında tartışmayı amaçladık.

Olgu

Otuz altı yaşında, 86 kg ağırlığında, multipar, 34 haftalık gebe hastaya plasental perkreta nedeniyle elektif sezaryen operasyonu planlandı. Hastanın özgeçmişinde supraventriküler taşikardi (SVT) nedeniyle kardiyak ablasyon yapılması dışında ek hastalığı yoktu. Gebeliğinin 29. Haftasında plasenta invazyon anomalisi tanısı konan ve yakın takip amacı ile hastanede yatılı takip edilen hastanın başvurusunda Hb: 9,58 g dl-1, Htc: % 27,9, fibrinojen: 402 mg/dL, ferritin: 2,85 ng/mL, demir: 36 ug/dL, total demir bağlama kapasitesi: 550 ug/dL, transferrin satürasyonu: %6,54 olması nedeniyle 1 g intravenöz (İV) demir (Ferriccarboxymaltose: FCM, Ferinject® 500 mg flakon, Abdi İbrahim, İstanbul) tedavisi uygulandı.

Hastanın preoperatif Hb: 9,64 g dl-1, Htc: %29,6, lökosit sayısı: 6,84 K/uL, trombosit sayısı: 200 K/uL idi. Hastaya standart monitörizasyonun [elektrokardiyogram, periferik oksijen satürasyonu, non-invazif kan basıncı (KB)] yanı sıra noninvazif intravasküler volüm takibi için Pleth Variability Index (PVI), hemoglobin takibi için SpHb (Masimo Radical7; Masimo Corporaiton, Irvine, CA, USA) ve anestezi derinliğinin takibi için de PSI (SEDLine, Masimo Corporaiton, Irvine, CA, USA) monitörizasyonu yapıldı. Preoperatif KB 116/65 mmHg, kalp atım hızı (KAH) 105 atım dk-1, PVI 25 ve SpHb 10,3 g/dL idi. Preoperatif aspirasyon profilaksisi amacıyla metoklopramid ve ranitidin İV uygulandı. Hastaya %100 oksijen ile 3 dakika preoksijenizasyon yapıldıktan sonra anestezi indüksiyonunda propofol 2 mg kg-1 ve roküronyum 1,2 mg kg-1 uygulanarak iç çapı 7,0 mm tüple endotrakeal entübasyon gerçekleştirildi. Anestezi idamesinde umbilikal kord klempleninceye dek %40/60 O2-hava içinde desfluran 0,75 MAK uygulandı. Analjezik olarak 0,25-0,05 mcg/kg/dk remifentanil infüzyonu başlandı. Genel anestezi indüksiyonundan 12 dakika sonra 2320 gram ağırlığında kız bebek doğdu, 1./5. dakika Apgar skorları sırasıyla 4/7 idi ve yenidoğan yoğun bakım ünitesine (YBÜ) götürüldü. Bebek doğduktan sonra desfluran 1 MAK olacak şekilde arttırıldı. Operasyonun 25. dk'sında kanamaya başlayan hastaya invazif KB ve arteryel kan gazı takibi amacıyla sağ radial arter kateterize edildi ve önce 1 g tranekzamik asit, kanamanın devam etmesi üzerine de 30 dk sonra 0,25 g ek doz İV yapıldı. KB'nın düşük seyretmesi üzerine noradrenalin infüzyonu başlandı. Cerrahi süresince toplam yaklaşık 3500 mL kanama oldu ve toplamda 3 Ü eritrosit süspansiyonu (ES), 2 Ü taze donmuş plazma (TDP), 1000 mL %0,9 NaCl, 500 mL jelatin ve 3 g fibrinojen konsantresi (Hamemocomplettan P®, 1000 mg flakon, CSL Behring, İstanbul, Türkiye), 2 ampul kalsiyum verildi. 3 saat süren operasyon sonunda noradrenalin infüzyonu ile birlikte KB 90/55 mmHg, KAH 110 atım/dk olan hasta entübe şekilde YBÜ'ye alındı.

Postoperatif 1.günde hipotansiyonun devam etmesi nedeniyle noradrenalin desteğine devam edildi. Hastadan kardiyoloji konsültasyonu istendi ve yapılan ekokardiyografide ejeksiyon fraksiyonu %35 %40 ve global sol ventrikül hipokinezi saptandı. Hastanın kalp yetmezliği tedavisine yönelik digoksin ve diüretik tedavisi başlandı. Postoperatif 2. günde hastanın noradrenalin desteği kesildi, Hb:7,5 g/dL, transferrin satürasyonu %12 olması sebebiyle 1 g İV demir uygulandı. Postoperatif 3. günde hemodinamisi stabil olan hasta servise devredildi.

Hastanın preoperatif ve postoperatif laboratuvar değerleri Tablo 1 ve 2'de sunulmuştur.

Tablo 1. İntraoperatif ve postoperatif arteryel kan gazı değerleri

	İntraoperatif (Kanama başladıktan sonra)		Postoperatif
	8. dakika	34. dakika	
PH	7.36	7.11	7.37
PCO2 (mmHg)	33.3	38.7	25.6
PO2 (mmHg)	98.0	203	131
Hb (g/dL)	9.1	9.3	8.6
K (mmol/L)	3.9	5.2	3.6
Na (mmol/L)	139	137	135
Ca (mmol/L)	1.14	1.19	1.23
Glukoz (mg/dL)	119	380	131
Laktat (mmol/L)	0.7	7.6	7.4
Baz açığı (mmol/L)	-5.8	-15.7	-9.4
HCO3 (mmol/L)	19.8	11.9	17.2

Tablo 2. Peroperatif loboratuvar değerleri

	Preoperatif	Postopertif 1. gün	Postopertif 2. gün
Hb (g/dl)	9,64	7,95	7,5
Htc (%)	29,6	22,8	23,1
Trombosit (K/uL)	200	175	156
Üre (mg/dl)	8	15	17
Kreatinin (mg/dl)	0,30	0,46	0,35
INR	1,05	1,27	1,25
Fibrinojen (mg/dl)	277	241	326

Tartışma

Serum ferritin düzeyinin <30 µg/L olması ya da CRP >5mg/L ve/veya transferrin satürasyonu <%20, ferritin <100 µg/L olması DEA tanısını koydurur. DEA'nın preoperatif dönemde tedavi edilmesi ile transfüzyon ilişkili komplikasyonların azaltılması amaçlanmalıdır [3]. Yapılan çalışmalarda parenteral demir tedavisinin, hamilelik sürecinde ve doğum sonrasında hemoglobin artışına ve demir depolarının yenilenmesine daha iyi katkı sağladığı bildirilmiştir [2,4]. Anemisi bulunan ve spinal anestezi altında sezaryen operasyonuna alınan bir gebede intraoperatif dönemde verilen tek doz İV demir tedavisi ile postoperatif DEA'nın hızlı düzeldiği bildirilmiştir [5]. Bizim hastamızın başvurusunda ferritin düzeyinin 2,85 ng/mL, transferrin satürasyonunun <%20 olması nedeniyle DEA tanısı ile hastamıza İV demir replasmanı uyguladık. Ayrıca postoperatif dönemde anemisi devam eden hastanın (Hb=7,5 g/dL) hemodinamisi stabil olması nedeniyle kan transfüzyonu yerine İV demir replasmanını tekrarladık.

Plasenta invazyon anomalileri çok yaygın olmamakla birlikte rutin gebelik takiplerinde saptanabilmektedir. Plasentanın koryonik villüslerinin uterus içine olan invazyon derecesine göre sırasıyla plasenta akreata, plasenta inkreata ve plasenta perkreta olarak adlandırılır [6]. Bizim olgumuzda gebeliğin 29. haftasında rutin USG kontrolü esnasında plasenta perkreta tanısı konulmuştur.

Avrupa Kalp Derneği Kalp Yetmezliği Birliği çalışma grubu PPKMP'yi gebelik sırasında veya sonrasında erken dönemde kalp yetmezliği ve sol ventrikül sistolik disfonksiyonu (sol ventrikül ejeksiyon fraksiyonu ≤ 45%) ile karakterize bir idiopatik KMP olarak tanımlamıştır [7]. Patogenezi hala tam olarak anlaşılamamış olmakla birlikte; gebelikle birlikte değişen hormon düzeyleri, ailesel ve genetik faktörler, hemodinamik değişiklikler ve IL-6 ve TNF-α gibi inflamatuar sitokinlerin patogenezde etkili oldukları gösterilmiştir [8]. Bizim olgumuzda hastamızın özgeçmişinde SVT nedeniyle kardiyak ablasyon dışında ek bir hastalığı olmamasına rağmen, nispeten ileri yaş gebelik olması ve anemi risk faktörleri olarak değerlendirilebilir. Ayrıca plasenta perkreta nedeniyle masif kanama ve kan ürünü transfüzyonu yapılması nedeniyle hızlı hemodinamik değişikliklerin olması ve inflamatuar sitokinlerin salınması nedeniyle de PPKMP gelişmiş olabilir.

Kardiyomyopati hastalarında anestezi tekniğinin seçimi klinik durum, hemodinamiyi sürdürme hedefine göre değerlendirilir. Sıklıkla nöroaksiyel anestezi uygulanmakla birlikte hastanın klinik durumuna bağlı olarak genel anestezi de uygulanabilmektedir [9,10]. Kliniğimizde perioperatif dönemde KMP tanısı bulunan hastalarda nöroaksiyel anestezi uygulamaktayız. Fakat bu hastada preoperatif dönemde KMP'yi düşündüren belirtinin bulunmaması ve plasental perkreta bağlı masif kanama beklentisi nedeniyle genel anestezi uygulamayı tercih ettik. Kanama beklentisi olduğundan dolayı intravasküler volüm takibi için PVI, noninvazif hemoglobin takibi, anestezi derinliğinin takibi için de PSI monitörizasyonu uyguladık. Akut kanama sırasında gelişen hipotansiyon ve periferik dolaşımın bozulması ile PVI, noninvazif hemoglobin değerleri görülemedi. Ancak operasyonun başından itibaren invazif arter monitörizasyonuna geçişimize kadar bize hastanın daha güvenilir bir şekilde takibini sağladı.

İnvaziv monitörizasyonlar genellikle operasyon sırasında hastanın klinik durumu değerlendirilerek yapılmaktadır. Bu hastada da noninvazif hemoglobin trend takibi yapılmasına rağmen hipotansiyon nedeniyle kan basıncının anlık değişimini takip edebilmek ve ardışık arteryel kan gazı örneği alabilmek amacıyla invazif arter monitörizasyonu yaptık. İntravasküler yeterli volüm replasmanına rağmen hipotansiyonun devam ettiği durumlarda inotropik ajanlarla kan basıncı kontrolü yapılabilmekte ve yeterli atım volümü sağlanabilmektedir [10]. Bizde bu hastada kalp atım hızı yüksekliğini de göz önünde bulundurarak noradrenalin infüzyonu kullandık ve yoğun bakımda postoperatif 2. güne kadar noradrenalin infüzyonunu kullanarak kan basıncı kontrolünü sağladık.

Sonuç

Tüm elektif cerrrahi planmalasında olduğu gibi gebelerde de preoperatif demir eksikliği anemisi mutlaka tedavi edilmelidir. Oral demir tedavisinin yetersiz kaldığı ya da operasyon öncesi sürenin kısıtlı olduğu durumlarda İV demir tedavisi uygulanmalıdır. Ayrıca, yüksek kanama riski olan sezaryenlerde standart monitörizasyonun yanı sıra uygulanan noninvazif ileri monitörizasyonlar; hastaların hemodinamik takiplerini daha iyi yapabilmemize olanak sağlamaktadır. Gebelerde preoperatif dönemde klinik semptomu olmasa bile intraoperatif ya da postoperatif dönemde PPKMP gelişebileceği her zaman akılda bulundurulmalıdır.

* Bu çalışma, Helsinki Deklarasyonuna göre yerel Etik Kurul tarafından değerlendirilerek onaylandı ve hastadan onam formu alındı.

Çıkar çatışması / finansal destek beyanı

Bu yazıdaki yazarların herhangi bir çıkar çatışması yoktur. Yazının herhangi bir finansal desteği yoktur.

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To cite this article: Korkmaz A, Demirtas B, Ozkan C, Yakici IE, Guray U. A huge aneurysm of the left main coronary artery in a patient presenting with acute anterior myocardial infarction. Turk J Clin Lab 2020; 4: 338-340.

Case Report

A huge aneurysm of the left main coronary artery in a patient presenting with acute anterior myocardial infarction

Akut anterior miyokard infarktüsü ile başvuran bir hastada distal sol ana koroner arterin dev anevrizması

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Abstract

Coronary artery aneurysms (CAAs) are uncommon clinical presentations associated with some acute and chronic complications. They are generally detected incidentally. Stasis in aneurysm may cause thrombosis and thus acute coronary syndrome. This manuscript presents a giant aneurysm of the LMCA observed in the coronary angiography of a 37-year-old female patient who was brought to emergency services due to cardiac arrest and whose electrocardiography (ECG) revealed acute anterior myocardial infarction.

Keywords: acute myocardial infarction; coronary artery aneurysm; left main coronary artery

Öz

Koroner arter anevrizmaları, bazı akut ve kronik komplikasyonlarla ilişkili, nadir görülen klinik tablolardır. Genellikle tesadüfen tespit edilirler. Anevrizma içerisindeki durgunluk tromboza ve dolayısıyla akut koroner sendroma neden olabilir. Bu yazıda kalp durması nedeniyle acil servise getirilen ve elektrokardiyografisinde akut anteriyor miyokard enfarktüsü saptanan 37 yaşındaki kadın hastanın koroner anjiyografisinde görülen devasa sol ana koroner arter (LMCA) anevrizması sunulmaktadır.

Anahtar Kelimeler: akut miyokard enfarktüsü, koroner arter anevrizması, sol ana koroner arter

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Recevied: 05.03.2020 accepted: 06.04.2020
Doi: 10.18663/tjcl.699469

Volume 11 Number 4 p: 338-340

Introduction

A coronary artery aneurysm (CAA) is identified as a 1.5-fold or more fusiform or sagittal enlargement of the normal coronary artery diameter.[1] It is usually caused by the right coronary artery (RCA); however, it may also involve the left anterior descending (LAD) artery, the circumflex artery (Cx) and occasionally the left main coronary artery (LMCA).[2] As it may be congenital, it may especially develop due to atherosclerosis, infection, trauma, vasculitis, Kawasaki disease, autoimmune diseases, postoperative, spontaneous dissection and metastatic tumors.[3-5] It is more common in men and the frequency of angiography ranges from 0.3 to 4.9 percent.[6] In this case, we present a 37-year-old female patient with SLE disease who had a giant aneurysm in LMCA who underwent coronary angiography upon detection of acute anterior myocardial infarction when she was brought to the emergency service after cardiac arrest.

Case

A 37-year-old female patient, who had been followed up with SLE diagnosis, was brought to the emergency services due to cardiac arrest that developed following chest pain. An acute anterior myocardial infarction was observed in the ECG taken after receiving a response to a cardiopulmonary resuscitation (CPR) performed in the emergency service. The patient was intubated and then taken into the catheterization laboratory, by applying CPR at intervals. A giant aneurysm of distal LMCA and with a thrombus inside were observed through coronary angiography. No flow was observed in the LAD and Cx arteries (Figure 1). Floppy wires were used to pass the LAD and Cx arteries. CPR-guided distal flow was achieved after performing repeated thrombus aspiration, intracoronary thrombolysis (Alteplase) and percutaneous transluminal coronary angioplasty (PTCA) (Figure 2). Nevertheless, no response was observed to extended CPR and the patient was pronounced dead.

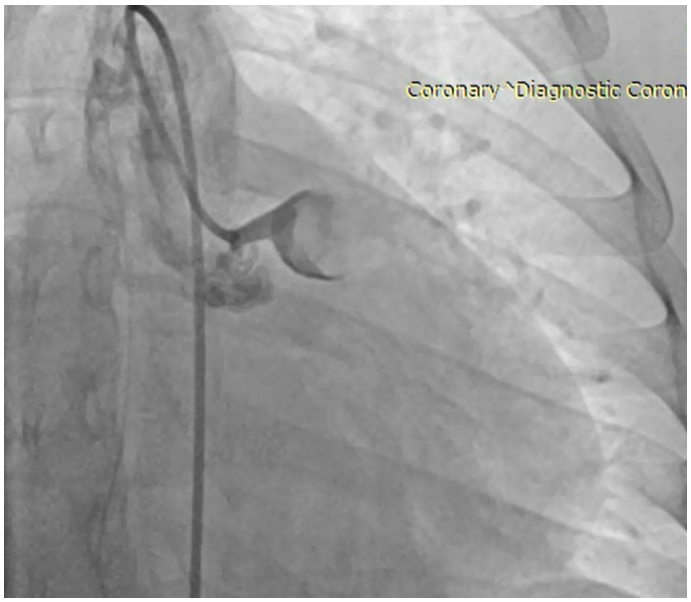

Figure 1: A giant aneurysm of distal LMCA and with a thrombus inside were observed through coronary angiography. No flow was observed in the LAD and Cx arteries.

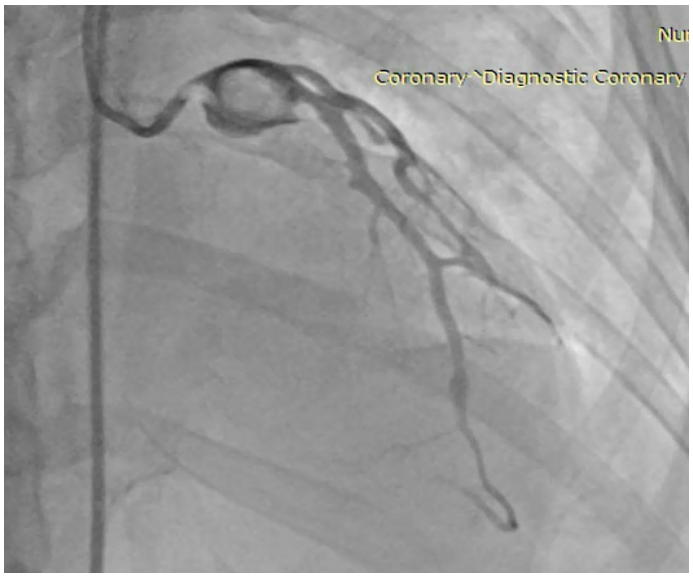

Figure 2: CPR-guided distal coronary flow was achieved after performing repeated thrombus aspiration, intracoronary thrombolysis and percutaneous transluminal coronary angioplasty.

Discussion

Coronary artery aneurysms (CAA) are associated with high morbidity and mortality rates. LMCA aneurysms are particularly difficult due to their anatomical location and involvement of multiple arterial branches. Affected patients are asymptomatic, but some are at risk of plaque rupture, dissection and other complications. Optimal management is uncertain and research into the optimal management of these vascular malformations continues.

Coronary aneurysm at LMCA location is encountered extremely rarely. Standard coronary angiography is the gold standard method for diagnostic purposes; however computed tomography and magnetic resonance angiography are being increasingly used for evaluation of such coronary aneurysms.[7-8] Most frequent causes include atherosclerosis, autoimmune diseases (Kawasaki disease, Systemic lupus erythematous (SLE), Takayasu disease), dissection, and trauma. [3-5] In our case SLE seems to be the most probable etiologic factor. Coronary artery aneurysms might cause various clinical problems. Our case presented with cardiac arrest due to acute myocardial infarction likely due to thrombotic occlusion and distal embolization, originating from the distal huge left main aneurysm. Other potential life threatening complication is rupture of coronary artery aneurysms.

Management of CAAs is controversial and generally depends on clinical presentation. Conservative or surgical approaches can both be recommended.[9] Medical therapy includes antiplatelet agents with/or without anticoagulants. Interventional therapies like covered stent to obliterate the aneurismal cavity was reported to be used with good short term outcome.[10] However current standard therapy is surgical revascularization with coronary artery bypass. [11] In acute occlusion situations, systemic or intracoronary fibrinolysis, thrombus aspiration and percutaneous coronary intervention techniques may be useful.

Conclusion

In conclusion, it may be suggested that coronary lesions should be screened in the follow-up and treatment of SLE, which may be a cause of acute myocardial infarction in young people.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

*This study was approved by our Institutional Review Board. Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

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To cite this article: Yazıcıoglu A., Simsek E., Yekeler E. Tufekcioglu O., Kaplan S An aberrant branch originating from right coronary artery leading to acute right heart failure and massive hemoptysis after cardiac surgery: A case report Turk J Clin Lab 2020; 4: 341-344.

Case Report

An aberrant branch originating from right coronary artery leading to acute right heart failure and massive hemoptysis after cardiac surgery: A case report

Kardiyak cerrahi sonrası, akut sağ kalp yetmezliği ve masif hemoptiziye sebep olan, sağ koroner arterden köken alan aberran dal: Olgu sunumu

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Abstract

Although there are several etiological factors for massive hemoptysis, necrosis and infarction of the lung parenchyma are rare causes. Herein, we describe a case of massive hemoptysis due to infarction and associated necrosis of the lung after cardiac surgery. The reason for necrosis was thrombosis of an aberrant artery originating from the right coronary artery and supplying the upper lobe of the left lung. The thrombosis was observed during an embolization procedure for cessation of hemoptysis. To the best of our knowledge, this is the first case in the literature to report an aberrant artery originating from the right coronary artery and supplying the left lung. Additionally, hemoptysis related to a vascular obstruction of an aberrant artery and related necrosis of parenchyma was uncommon. Finally, an acute right heart failure related to the obstruction of aberrant artery was also uncommon.

Keywords: aberrant artery; coronary artery; hemoptysis; infarction; right heart failure

Öz

Masif hemoptizi için pek çok etyolojik neden bulunmasına karşın akciğer parankiminin enfarktı ve nekrozuna bağlı hemoptizi nadirdir. Bu sunumda, kardiyak cerrahi sonrası akciğer enfarktı ve nekrozuna bağlı masif hemoptizi olgusu sunulmuştur. Akciğer parankimindeki nekrozun nedeni, sağ koroner arterden köken alan ve sol akciğer üst lobunu besleyen aberran arterin trombozu idi. Tromboz, hemoptizi tedavisi için uygulanan embolizayon işlemi sırasında fark edildi. Literatür taramasında, sağ koroner arterden çıkan aberran dalın sol akciğer üst lobunu beslediği başka olgu bulunmamaktadır. Ayrıca, aberran dalın obstrüksiyonu ve buna bağlı olarak parankim nekrozuna sekonder hemoptizi de nadirdir. Son olarak, aberran dalın obstrüksiyonuna bağlı akut sağ kalp yetmezliği de nadir olarak görülmektedir.

Anahtar kelimeler: aberran arter; koroner arter; hemoptizi; enfarkt; sağ kalp yetmezliği

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Recevied: 23.03.2020 accepted: 12.06.2020
Doi: 10.18663/tjcl.707535
*This abstract has been accepted as a poster session in the World Society of Cardiothoracic Surgeons, 27th Congress, which held at Astana-Kazakhstan, between 1-3 September 2017.

Volume 11 Number 4 p: 341-344

Introduction

Massive hemoptysis is a potentially serious and life-threatening condition due to the blood asphyxiation and may cause sudden airway obstruction and hemodynamic instability [1]. Several diseases have been shown to play a role in the etiology of massive hemoptysis including bronchiectasis, infectious lung diseases, and lung cancer [1]. However, the thrombosis of abnormal vascular structures and hemorrhage associated with the necrosis of the lung parenchyma supplied by the obstructed abnormal vascular structure is a rare condition.

In this article, we report a rare case of an aberrant branch originating from the right coronary artery (RCA) and supplying the upper lobe of the left lung which led to acute right heart failure and massive hemoptysis after cardiac surgery.

Case

A 43-year-old female patient underwent mitral valve replacement (MVR) due to severe mitral regurgitation. Her medical history revealed that she had minor hemoptysis which was evaluated by the chest diseases department and no underlying pulmonary pathology was found and mitral regurgitation was considered for the main reason for hemoptysis. Echocardiography (ECHO) results were detailed in Table-1. In the preoperative workup, coronary angiography did not reveal an atherosclerotic plaque in the coronary arteries, and a vessel branch originating from the RCA was observed to supply the upper lobe of the left lung (Figure-1a). During MVR surgery, the vessel branch originating from the RCA and supplying the upper lobe of the left lung was not dissected and was not ligated. During surgery, cross-clamping was simultaneously performed to the aortic and pulmonary arteries. Following left atriotomy, an excessive backflow from the pulmonary venous system was observed, despite double cross-clamping. Surgery was successfully completed, and the patient was uneventfully weaned from cardiopulmonary bypass. During intensive care unit (ICU) follow-up, arrhythmia with tachycardia and bradycardia episodes developed. A temporary pacemaker was inserted. Due to arrhythmias and respiratory problems, the length of ICU stay prolonged and the patient was discharged from the ICU on postoperative Day 6.

Table-1: Echocardiography (ECHO) results of patient.

Parameter	ECHO Result
Mitral valve area	2.1 cm2
Maximum/mean gradient of the mitral valve	12/4 mmHg
Systolic pulmonary artery pressure (sPAP)	55 mmHg
Left ventricular end diastolic diameter (LVEDD)	5.6 cm
Left ventricular end systolic diameter (LVESD)	3.9 cm
Interventricular septum	1.0 cm
Ejection fraction (EF)	57%
Tricuspid annular plane systolic excursion (TAPSE)	>2cm
Left atrial diameter	4.3 x 5.6 cm
Valves	Fibrotic mitral valve, Third-degree mitral regurgitation, First- to second-degree tricuspid regurgitation.

During the ward follow-up, the patient suffered from a sudden massive hemoptysis on postoperative Day 7 (>600mL/day). The international normalized ratio (INR) was between 2.3 and 2.8, activated partial thromboplastin time (aPTT) was between 28 and 32 sec, and platelet count was between 170.000 and 230.000 count/µL, without any hematological problem. Warfarin was ceased and the INR decreased with fresh frozen plasma, while low-molecular-weight heparin was added to the treatment. The amount of hemoptysis decreased to 300mL/day; however, no cessation was observed. On the next day, a thoracic computed tomography (CT) revealed a consolidated area in the posterior segment of the left upper lobe of the lung, and the etiology of hemorrhage was considered to be associated with the vessel branch originating from the RCA and supplying the left upper lobe of the lung (Figure-2a,b). Considering that this aberrant branch might play a role in the etiology of hemoptysis and interruption of the blood flow in this branch might lead to hemoptysis cessation, selective embolization was planned for this vessel branch. However, thrombosis was detected in this vessel branch during catheterization (Figure-1b). In this case, the etiology of hemorrhage was found to be thrombosis of the aberrant artery and associated infarction of the upper lobe of the left lung, and hemoptysis was secondary to the infarction. Conservative treatment modalities were used. The amount of hemoptysis decreased within a couple of days and ceased on postoperative Day 8. During follow-up, the mean pulmonary artery pressure (mPAP) increased, and physical examination showed peripheral edema. The patient was given medical treatment and discharged on postoperative Day 25 with resolution of edema.

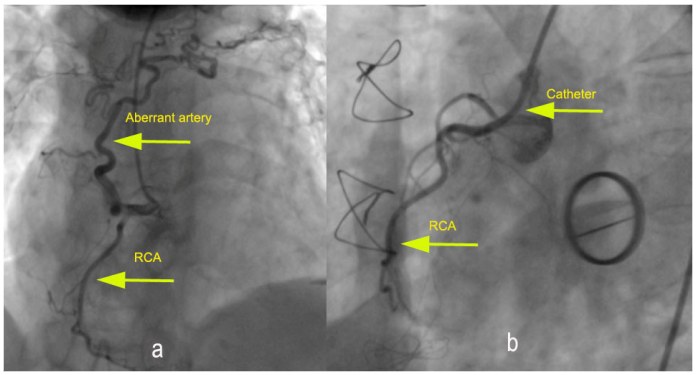

Figure 1(a): During preoperative cardiac catheterization, a vessel branch originating from right coronary artery was supplying left upper lobe, **(b):** However, after hemoptysis, trombosis was observed in this vessel during catheterization.

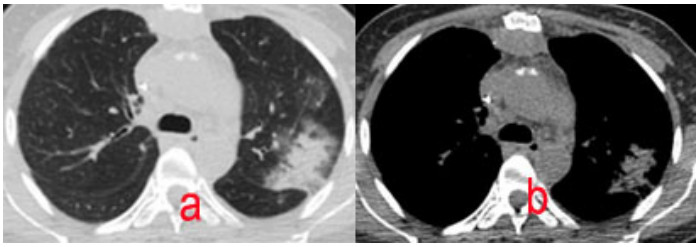

Figure 2 (a,b): Thoracic CT revealed consolidated area in the posterior segment of the left upper lobe.

At three months of follow-up, the patient was readmitted with symptoms and signs of right heart failure including peripheral edema, ascites, lip cyanosis, fatigue, and hepatomegaly. Repeated ECHO revealed non-coaptation of the tricuspid valve with significant tricuspid regurgitation (3-4) and pulmonary insufficiency (2-3), a mPAP of 40 mmHg, a TAPSE of 1.4 cm, and significantly enlarged right heart chambers. During right heart catheterization, the pulmonary capillary wedge pressure was 16 mmHg with a sPAP of 36 mmHg, a diastolic pulmonary arter pressure of 14 mmHg, and a mPAP of 24 mmHg, In addition, the pulmonary vascular resistance was 2 wood, cardiac output was 3.96 L/min, and cardiac index was 2.16 L/min/m2. Chest perfusion scintigraphy showed significantly reduced perfusion of the upper lobe of the left lung. Simultaneously, follow-up thoracic CT revealed normal parenchyma in the posterior segment of the left upper lobe. Furthermore, the right ventricular assist device implantation was planned in the cardiovascular surgery clinic of an external center; however, the patient died at eight months due to right heart failure before the implantation.

Discussion

Hemoptysis should not be solely evaluated in terms of the volume of bleeding, and the life-threatening airway obstruction and asphyxiation should be considered. The anatomical dead space of the tracheobronchial tree is only 150 to 200 mL, and acute expectoration of only 200 mL may cause respiratory failure with altered hemodynamic states [1]. Yazicioglu et al. reported that bronchiectasis was the most common etiology of massive hemoptysis, followed by bronchial cancer, arteriovenous malformations, and infectious diseases of the lung [1]. However, pulmonary infarction and necrosis in the etiology of massive hemoptysis is uncommon. Hemoptysis related with necrosis of the lung parenchyma was frequently associated with necrotizing pneumonia of the lungs [2]. The lungs are the uncommon sites of infarctions secondary to vascular obstruction due to the presence of tissues enriched with blood flow from both the pulmonary and systemic circulation. Therefore, hemoptysis secondary to vascular obstruction is also rare.

Although the lungs may receive abnormal branches originating from a large number of arterial structures (i.e., subclavian, internal mammary, and vertebral arteries), branches originating from the coronary artery are rarely seen [3,4,5]. Battal et al. reported an incidental multi-detector computed tomography (MDCT) angiography finding of an aberrant right bronchial artery originating from the RCA [4]. However, an aberrant artery originating from the RCA and supplying the left lung was not reported previously. Our case is, therefore, unique and the branch from RCA was supplied the upper lobe of the left lung.

Abnormal vascular structures may also play a role in the etiology of hemoptysis, although pulmonary infarction is considered in the etiology of hemoptysis. Hwang et al. reported a case of massive hemoptysis from an aberrant bronchial artery originating from the descending thoracic aorta [5]. The authors treated the patient with endovascular bronchial artery embolization with a stainless steel platinum coil [5]. Gypen et al. reported an hemoptysis case previously had coronary artery bypass grafting with internal mammary artery had aberrant bronchial vessels [6]. In previous reports, bronchial and/or aberrant artery embolization with a coil

implantation was also the initial treatment method of massive hemoptysis [1,6,7]. The success rates of embolization were reported as 70 to 95% [7].

In our case, the upper lobe of the left lung was supplied by the aberrant artery originating from the RCA. In this case, the aberrant branch was suspected in the etiology of hemoptysis and, therefore, we planned aberrant artery embolization. However, during the embolization procedure, we detected thrombosis in the aberrant artery, which thrombosis probably occurred during MVR surgery. With the interruption of the blood supply, necrosis and infarction occurred in the supplied lung area and, therefore, hemoptysis was associated with the necrosis.

The differential diagnosis poses certain challenges in such cases. In the differential diagnosis, the elevated values of INR, decreased counts of platelets, or any other hematological problems may play a role in the development of hemoptysis. In our case, there was no significant increase in the INR and the platelet count was adequate without any hematological abnormalities. Although the INR was 2.3 to 2.8, it was attempted to be decreased. Despite the intervention, however, hemoptysis persisted and interruption of the blood supply from the aberrant artery via embolization was considered to discontinue bleeding. However, the lack of blood flow in the aberrant vessel during catheterization for embolization suggested another etiological cause. Therefore, several underlying causes of hemoptysis were suspected in the differential diagnosis and the exact cause was elucidated using different interventions.

Conclusion

Although hemoptysis associated with an abnormal vascular structure has been frequently reported in the literature, hemoptysis associated with the obliteration of the abnormal vascular structure is scarce. In patients with aberrant branch supplying the lungs, the possibility of hemoptysis associated with infarction or necrosis due to the obliteration of the aberrant branch and interruption of the blood flow after surgical manipulation should be kept in mind. The definite diagnosis is based on the catheterization, which is the gold standard technique, and embolization should be considered in the presence of blood flow in the aberrant artery. Otherwise, conservative methods can be used, as there may be other causes of hemoptysis to be considered. Also, clinicians should consider possible infarction and necrosis in the differential diagnosis of hemoptysis.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

*This study was approved by our Institutional Review Board. Informed consent was obtained from patient and the principles of the Helsinki Declaration were followed.

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TURKISH JOURNAL of CLINICS and LABORATORY

Türk Klinik ve Laboratuvar Dergisi

Turkish Journal of Clinics and Laboratory - Türk Klinik ve Laboratuvar Dergisi

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org internet adresinde bulabilirsiniz

Amaç ve kapsam: "Turkish Journal of Clinics and Laboratory", hakemli, açık erişimli ve periyodik olarak çıkan, DNT Ortadoğu Yayıncılık A.Ş. ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Yılda dört kez çıkan bir bilimsel bir tıp dergisidir. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org adresinden ulaşılabilir) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazılarıları yayımlayan bilimsel, uluslar arası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

On-line makale gönderimi: Tüm yazışmalar ve yazı gönderimleri dergipark üzerinden http://dergipark.gov.tr/tjcl yapılmalıdır. Yazı gönderimi için detaylı bilgi bu internet adresinden edinilebilir. Gönderilen her yazı için özel bir numara verilecek ve yazının alındığı e-posta yolu ile teyid edilecektir. Makalelerin "full-text" pdf formuna http://dergipark.gov.tr/tjcl linkinden ulaşılabilir.

Açık erişim politikası: Turkish Journal of Clinics and Laboratory açık erişimi olan bir dergidir. Kullanıcı lar yazıların tam metnine ulaşabilir, kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

Yazarlara Bilgi: Yazıların tüm bilimsel sorumluluğunu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayınlanan yazılar için herhangi bir sorumluluk kabul etmez.

Dergi adının kısaltması: Turk J Clin Lab

Yazışma adresi: Yazılar e-mail yoluyla sorumlu yazar tarafından, Dergipark ta yer alan Turkish Journal of Clinics and Laboratory linkine girip kayıt olduktan sonra gönderilmelidir.

Makale dili: Makale dili Türkçe ve İngilizcedir. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

Makalenin başka bir yerde yayımlanmamıştır ibaresi: Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

Değerlendirme: Dergiye gönderilen yazılar format ve plagiarism açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

Basıma kabul edilmesi: Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Her yazı için bir doi numarası alınır.

Yayın hakları devri: http:/www.dergipark.ulakbim.gov.tr/tjclinlab adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

Makale genel yazım kuralları: Yazılar Microsoft Word programı (7.0 ve üst versiyon) ile çift satır aralıklı ve 12 punto olarak, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçede ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

Yazının bölümleri

1. Sunum sayfası: Yazının Turkish Journal of Clinics and Laboratory 'de yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

2. Başlık sayfası: Sayfa başında gönderilen makalenin kategorisi belirtilmedir (Klinik analiz, orijinal çalışma, deneysel çalışma, olgu sunumu vs).

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik ve şehir yazar isimleri altına eklenmelidir.

Bu sayfada "sorumlu yazar" belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir.

Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

3. Makale dosyası: (Yazar ve kurum isimleri bulunmamalıdır)

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir.

Özet: Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

Anahtar kelimeler: Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

Metin bölümleri: Orijinal makaleler; Giriş, Gereç ve Yöntemler, Bulgular, Tartışma olarak düzenlenmelidir. Olgu sunumları; Giriş, Olgu sunumu, Tartışma olarak düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli metin içine yerleştirilmemelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Tablolar metin sonuna eklenmelidir. Resimler/fotoğraf kalitesi en az 300dpi olmalıdır.

Etik kurallar: Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Yöntem ve Gereçler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklerasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Turkish Journal of Clinics and Laboratory gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Teşekkür yazısı: Varsa kaynaklardan sonra yazılmalıdır.

Maddi destek ve çıkar ilişkisi: Makale sonunda varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmelidir. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www.icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya DOI numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları "Cumulated Index Medicus" ta kullanılan stile uymalıdır. Kaynak sayısının araştırmalarda 25 ve derlemelerde 60, olgu sunumlarında 10, editöre mektupta 5 ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce köşeli parantez kullanılarak belirtilmelidir. Örneğin [4,5]. Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

Şekil ve tablo başlıkları: Başlıklar kaynaklardan sonra yazılmalıdır.

4. Şekiller: Her biri ayrı bir görüntü dosyası (jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra "Dizginin ilk düzeltme nüshası" sorumlu yazara e-mail yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-mail ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Özpolat B, Gürpınar ÖA, Ayva EŞ, Gazyağcı S, Niyaz M. The effect of Basic Fibroblast Growth Factor and adipose tissue derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end to end anastomosis rat model. Turk Gogus Kalp Dama 2013; 21: 1010-19.

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998:1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag;1988:45-67.

Doktora/Lisans Tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, ulaşım tarihi detaylı olarak verilmelidir.

DOI numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of Complementary and Alternative Medicine into Family Practice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

Bilimsel sorumluluk beyanı: Kabul edilen bir makalenin yayınlanmasından önce her yazar, araştırmaya, içeriğinin sorumluluğunu paylaşmaya yetecek boyutta katıldığını beyan etmelidir. Bu katılım şu konularda olabilir:

a. Deneylerin konsept ve dizaynlarının oluşturulması, veya verilerin toplanması, analizi ya da ifade edilmesi;

b. Makalenin taslağının hazırlanması veya bilimsel içeriğinin gözden geçirilmesi

c. Makalenin basılmaya hazır son halinin onaylanması.

Yazının bir başka yere yayın için gönderilmediğinin beyanı: "Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayınlanmadığını, ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim. Bu, 400 kelimeye kadar olan özetler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir."

Sponsorluk beyanı: Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı

2. Veri toplanması, analizi ve sonuçların yorumlanması

3. Raporun yazılması

Kontrol listesi:

1. Editöre sunum sayfası (Sorumlu yazar tarafından yazılmış olmalıdır)

2. Başlık sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Yazarlar, kurumları, sorumlu yazar posta adresi, tüm yazarların e-mail adresleri, sorumlu yazarın telefon numarası)

3. Makalenin metin sayfası (Makale başlığı/kısa başlık Türkçe ve İngilizce, Özet/anahtar kelimeler, Summary/keywords, makale metni, kaynaklar, tablo ve şekil başlıkları, tablolar, şekiller)

4. Tablo ve grafikler metin içinde olmalıdır.

5. Şekiller (En az 300 dpi çözünürlükte) ayrı bir veya daha fazla dosya halinde gönderilmelidir.