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Önsöz

Değerli Okuyucularımız,

Atatürk Üniversitesi Tıp Fakültesi Cerrahi Tıp Bilimleri Dergisi'nin Ağustos 2024 sayısını yayınlıyoruz. Bu sayımız, tıp biliminin çeşitli alanlarında önemli katkılarda bulunan özgün makaleler, meta-analizler ve olgu sunumlarıyla zenginleştirilmiştir.

Bu sayımızda sunulan *"Kronik Ağrılı Hastalarda Spinal Kord Stimülasyonu Uygulamasının Uyku, Yaşam Kalitesi, Anksiyete ve Depresif Semptomlar Üzerine Etkisi"* başlıklı çalışma, spinal kord stimülasyonunun kronik ağrı yönetimindeki etkilerini kapsamlı bir şekilde ele almaktadır. Ağrı tedavisinde bu yöntemlerin, özellikle uyku kalitesi ve yaşam kalitesi üzerindeki etkileri, hekimler ve araştırmacılar için önemli bilgiler sunmaktadır.
"Lateral Dekübit Pozisyonunda Hacim Kontrollü Ventilasyon Modu ve Hacim Garantili Basınç Kontrollü Ventilasyon Modlarının Değerlendirilmesi: Randomize Kontrollü Çalışma" başlıklı makale, ventilasyon stratejilerinin hemodinamik ve solunum parametreleri üzerindeki etkilerini karşılaştırarak, klinik uygulamalarda hangi ventilasyon modunun daha uygun olabileceğine dair değerli veriler sunmaktadır. Lateral pozisyondaki etkilerin detaylı analizi, solunum desteği ihtiyacı olan hastalar için önemli bir kılavuz olacaktır.
"Pineal Gland Kalsifikasyonu ile İndüklenmiş Olfaktör Bulbus Lezyonu: İlk Deneysel Çalışma" başlıklı özgün makale, pineal bez kalsifikasyonlarının olfaktör bulbus üzerindeki etkilerini incelemekte ve bu konudaki ilk deneysel çalışmalardan biri olarak bilimsel literatüre katkı sağlamaktadır.

"Total diz artroplastisi sonrası lokal soğuk uygulamanin etkisi: sistematik inceleme" başlıklı çalışma ile de diz cerrahisi sonrası soğuk uygulamanın etkinliğinin bir meta-analiz ile değerlendirilmesi okuyucularımızın nazarına sunulmuştur.

Olgu sunumları bölümümüzde ise dikkat çeken üç çalışma yer almaktadır:

"Orbital Dev Soliter Fibroz Tümörün Subkonjunktival Yaklaşım ile Rezeksiyonu: Olgu Sunumu", nadir bir

Preface

Dear Readers;

Atatürk University Faculty of Medicine, Journal of Surgical Medical Sciences August 2024 issue is now published. This issue is enriched with original articles, meta-analysis and case reports that make significant contributions in various fields of medical science.

In this issue, the study titled *"The effects of spinal cord stimulation on sleep, quality of life and anxiety and depressive symptoms in patients with chronic pain"* comprehensively addresses the effects of spinal cord stimulation in chronic pain management. The effects of these methods, especially on sleep quality and quality of life, provide important information for physicians and researchers.

The article titled *"Evaluation of volume controlled ventilation mode and volume guaranteed pressure controlled ventilation modes in lateral decubitus position; randomized controlled study"* provides valuable data on which ventilation mode may be more appropriate in clinical practice by comparing the effects of ventilation strategies on hemodynamic and respiratory parameters. The detailed analysis of the effects in the lateral position will be an important guide for patients needing respiratory support.

The original article titled *"Olfactory bulb lesion induced pineal gland calcification: a first experimental study"* examines the effects of pineal gland calcifications on the olfactory bulb and contributes to the scientific literature as one of the first experimental studies on this subject.

The study titled *"The effect of local cold application after total knee arthroplasty: a systematic review"* presents to our readers an evaluation of the effectiveness of cold application after knee surgery through a meta-analysis.

In our case reports section, four noteworthy studies are featured:

The case report titled *"Giant solitary fibrous tumour of the orbit resected via subconjunctival approach: case*

orbital tümörün başarılı bir şekilde subkonjunktival yaklaşım ile nasıl çıkarıldığını detaylandırmaktadır.

"Düşük Doz Steroid Tedavisi Sonrası Gelişen CMV Reaktivasyonu: Olgu Sunumu", düşük doz steroid tedavisinin CMV reaktivasyonuna etkilerini ve yönetim stratejilerini kapsamlı bir şekilde ele almaktadır.
"Rekürrens ile Gelen Sıtma Olgusu", tekrarlayan sıtma vakalarının tanı ve tedavi sürecindeki zorlukları gözler önüne sermektedir.

Bu sayımızdaki çalışmalar ve olgu sunumları, cerrahi tıp biliminin farklı alanlarında değerli bilgiler sunmakta, klinik pratiğe ve bilimsel araştırmalara önemli katkılar sağlamaktadır. Dergimize katkıda bulunan tüm yazarlarımıza, hakemlerimize ve okuyucularımıza teşekkür ederiz. Bilimin ve bilginin ışığında, cerrahi tıp alanındaki en güncel bilgileri sizlerle paylaşmaya devam edeceğiz.

Saygılarımla

Baş Editör
Doç Dr Sevilay ÖZMEN

report" details how a rare orbital tumor was successfully removed using a subconjunctival approach.
The case report titled *"A case report of cmv reactivation after low dose steroid treatment"* comprehensively addresses the effects of low-dose steroid therapy on CMV reactivation and management strategies.
The case report titled *"Recurrence malaria: a case report"* highlights the challenges in the diagnosis and treatment process of recurring malaria cases.

The studies and case reports in this issue provide valuable information in various areas of surgical medical science, making significant contributions to clinical practice and scientific research. We thank all our authors, reviewers, and readers for their contributions. We will continue to share the most current information in the field of surgical medicine under the light of science and knowledge.

Kind regards

Chief Editor
Associate Professor Sevilay ÖZMEN

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Research Article *Araştırma Makalesi* DOI: 10.61745/ jsmsau.1464941

The Effects of Spinal Cord Stimulation on Sleep, Quality of Life and Anxiety and Depressive Symptoms in Patients with Chronic Pain

Kronik Ağrılı Hastalarda Spinal Kord Stimülasyonu Uygulamasının Uyku, Yaşam Kalitesi, Anksiyete ve Depresif Semptomlar Üzerine Etkisi

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ABSTRACT

Objective: The aim of this study was to investigate whether spinal cord stimulation (SCS), a neuromodulation technique, causes any changes in sleep, quality of life, anxiety and depressive symptoms before and after the procedure in patients with chronic pain.

Methods: The study was completed with 14 patients who were planned to undergo SCS for treatment-resistant chronic neuropathic pain and who applied to the psychiatry outpatient clinic for pre-treatment consultation. Patients were evaluated twice, before and 1 month after treatment. Patients were evaluated with LANNS Pain Scale, Hamilton Depression Scale (Ham-D), Hamilton Anxiety Scale (HAM-A), Pittzburg Sleep Quality Inventory (PUKI), and Quality of Life Scale Short Form (WHOQOL-Bref). Scale scores before and after the treatment were compared using a two-sample dependent t-test.

Results: Depressive disorder was detected in 85.8% of the cases, anxiety disorder in 71.5%, and sleep disorder in 78.6%. The cases' LANSS pain scale scores were 19.00±5.11 pre-treatment and 7.57±4.59 post-treatment, the difference being statistically significant (P=0.001). Significant differences were observed between pre- and post-test HAM-D, HAM-A, PSQI, quality of life (QoL) general health, QoL physical health, or QoL psychological health scores (*P*=.002, *P*=.014, *P*=.002, *P*=.002, *P*=.002, and *P*=.001, respectively). However, no significant differences were determined between pre- and post-test QoL social relationships or QoL environmental health scores (*P*=.160 and *P*=.831, respectively)

Conclusion: Our data in this study suggest that SCS not only effectively reduces pain in treatment-resistant chronic pain, but also mediates significant improvements in sleep quality, anxiety and depressive states.

Keywords: Chronic pain, spinal cord stimulation, sleep, quality of life, anxiety, depression

ÖZ

Amaç: Bu çalışmanın amacı, bir nöromodülasyon tekniği olan omurilik stimülasyonunun (SCS) kronik ağrılı hastalarda işlem öncesi ve sonrasında uyku, yaşam kalitesi, anksiyete ve depresif belirtilerde herhangi bir değişikliğe neden olup olmadığını araştırmaktır.

Yöntem: Çalışma, tedaviye dirençli kronik nöropatik ağrı nedeniyle SCS yapılması planlanan ve tedavi öncesi konsültasyon için psikiyatri polikliniğine başvuran 14 hasta ile tamamlandı. Hastalar tedaviden önce ve tedaviden 1 ay sonra olmak üzere iki kez değerlendirildi. Hastalar LANNS Ağrı Ölçeği, Hamilton Depresyon Ölçeği (Ham-D), Hamilton Anksiyete Ölçeği (HAM-A), Pittzburg Uyku Kalitesi Envanteri (PUKI), Yaşam Kalitesi Ölçeği Kısa Formu (WHOQOL-Bref) ile değerlendirildi. Tedavi öncesi ve tedavi sonrası ölçek puanları bağımlı iki örnekli t testi kullanılarak karşılaştırıldı.

Bulgular: Olguların %85,8'inde depresif bozukluk, %71,5'inde anksiyete bozukluğu, %78,6'sında uyku bozukluğu saptandı. Olguların LANSS ağrı skalası skorları tedavi öncesi 19,00±5,11, tedavi sonrası 7,57±4,59 idi ve aradaki fark istatistiksel olarak anlamlıydı (*P*=,001). Ön test ve son test HAM-D, HAM-A, PUKİ, yaşam kalitesi (QoL), genel sağlık, QoL fiziksel sağlık veya QoL psikolojik sağlık puanları arasında anlamlı farklılıklar gözlendi (*P*=,002, *P*=,014, *P*= ,002, *P*=,002, *P*=,002 ve *P*=,001 sırasıyla). Ancak ön test ve son test QoL sosyal ilişkiler veya QoL çevre sağlığı puanları arasında anlamlı farklılık saptanmadı (sırasıyla *P*=,160 ve *P*=,831)

Sonuç: Bu çalışmadaki verilerimiz, SCS'nin tedaviye dirençli kronik ağrıda sadece ağrıyı etkili bir şekilde azaltmakla kalmadığını, aynı zamanda uyku kalitesi, anksiyete ve depresif durumlarda da önemli iyileşmelere aracılık ettiğini göstermektedir.

Anahtar Kelimeler: Kronik ağrı,omurilik stimülasyonu, uyku, yaşam kalitesi, anksiyete, depresyon.

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INTRODUCTION

Chronic pain is a condition with a duration exceeding three months, requiring a multifaceted and multifactorial therapeutic approach, which may include emotional, cognitive and motivational compromise, and may be characterized by impaired functioning in all areas and decreased quality of life. [1] It is one of the leading causes of disability worldwide and affects approximately 20% of the global population. [2] Since chronic pain leads to impaired functioning, it causes significant socioeconomic effects on both the patient and the society, in addition to its negative effects on sleep and quality of life parameters. [3] Therefore, prevention of chronic pain is as important as rehabilitation in terms of public health. [4]

Chronic pain is frequently accompanied by sleep disorders. [5] Pain may be both the cause and the consequence of sleep disturbance. The presence of pain leads to sleep disturbance and depressive symptoms, while pain is experienced more severely in the presence of sleep disturbance and depression and this continues as a vicious cycle. [6] The physical and psychological effects of chronic pain also affect quality of life. [7] Studies emphasize the relationship between mood disorders and acute and/or chronic pain. Prolonged exposure to pain also leads to deterioration of the mental state. At the same time, anxiety and depression seem to be associated with more severe perception and less tolerance of pain.

Chronic neuropathic pain is one of the important causes of chronic pain. Shoulder pain and failed back surgery syndrome are the two leading causes of chronic neuropathic pain. [6] Neuromodulation is a relatively safe option in the treatment of chronic pain due to its low side effects and potential reversibility. Spinal cord stimulation (SCS), one of the neuromodulation techniques, has come to represent the basis of pain management in a large number of chronic painful conditions, including refractory radiculopathy, chronic regional pain syndrome, postoperative chronic pain, and especially failed lumbar surgery syndrome. [9] In recent years, its use has also increased in painful chronic conditions such as epidural fibrosis, post herpetic neuralgia, reflex sympathetic dystrophy, phantom pain, malignancy pain associated with vertebral metastases, and faecal and urinary incontinence. [10] In SCS, a low-voltage electric current is applied to the spinal cord. This prevents the transmission of pain in the relevant region to the central nervous system. It is performed using electrodes connected to the epidural space posterior to the dorsal columns of the spinal cord. These electrodes are connected to different levels of the spinal cord depending on the site of pain and connected to a pulse generator placed under the skin. [11]

It seems inevitable that this bidirectional interaction between chronic pain and sleep, anxiety, and depression will progress as a vicious cycle and negatively affect quality of life. Based on the idea that reducing or eliminating pain with SCS applications is the most radical solution to break this vicious cycle, we planned this study. The aim of this study is to examine whether SCS application causes any changes in sleep quality, anxiety and depression symptoms before and after the procedure in patients with chronic pain and how it affects quality of life. Our hypothesis was that sleep and quality of life would improve following SCS, and that anxiety and depressive symptoms would decrease.

METHODS

Ethical issues: The study was approved by the Erzurum Regional Training and Research Hospital ethical committee, Turkey (decision no. 2022/17-160 dated 07.11.2022). It was conducted in compliance with international declarations and guidelines.

Data collection: This study was conducted at Erzurum City Hospital between December 2022 and December 2023. Patients with treatment-resistant chronic neuropathic pain after failed back surgery syndrome (BBCS) who were planned to undergo SCS for pain management were included in the study. Twenty-three male and female patients between the ages of 18-65 years who applied to the psychiatry clinic for psychiatry consultation before SCS treatment and who volunteered to participate in the study and signed the informed consent form were included in the study. The patients were evaluated twice, before and one month after treatment. Nine patients were excluded for failing to take part in the post-treatment evaluation. The study was thus concluded with 14 patients. The participants were assessed using a sociodemographic data form, the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale, the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), the Pittsburg Sleep Quality Index (PSQI), and the World Health Organization Quality of Life Brief Version (WHOQOL-Bref).

Data Collection Tools: Sociodemographic Data Form: This was used to investigate the participants' sociodemographic and clinical characteristics and histories.

LANSS Pain Scale: This tool was developed by Bennett. [12] The validity and reliability of the Turkish-language version were confirmed by Yücel et al. in 2004. It is used in the evaluation of neuropathic pain and in differentiating neuropathic pain

and nociceptive pain. [13]

Pittsburgh Sleep Quality Index (PSQI): This scale was developed by Buysse et al. for the evaluation of sleep quality. [14]The validity and reliability of the Turkish-language version were confirmed by Ağargün et al. in 1996. [15] The scale's Cronbach's alpha reliability coefficient is 0.804.

World Health Organization Quality of Life Brief Version (WHOQOL-Bref): This scale was developed by the WHOQOL Group as a shorter version of WHOQOL-100 produced by the same group. [16]It consists of four domains, physical health, psychological health, social relationships, and environmental health. The validity and reliability of the Turkish-language version were established by Eser et al. [17] The scale's Cronbach alpha reliability values are 0.83 for physical health, 0.66 for psychological health, 0.53 for social relationships, and 0.73 for environmental health.

Hamilton Depression Rating Scale (HAM-D): This tool was developed by Hamilton for the purpose of evaluating depressive symptoms and severity.[18] The validity and reliability of the Turkish-language version were established by Akdemir et al. [19]

Hamilton Anxiety Rating Scale (HAM-A): This scale was developed by Hamilton for the determination of anxiety symptoms and severity. [20] The validity and reliability of the Turkish-language version were established by Yazıcı et al. [21]

Statistical Analysis

Statistical analyses were carried out on IBM SPSS version 22.0 software (IBM SPSS Corp., Armonk, NY,). Normality of distribution of the study variables was checked using the Kolmogorov-Smirnov and histogram tests. Descriptive data were expressed as mean ± standard deviation (SD). Categorical variables were analysed using the chi-square test. Non-normally distributed variables were analysed using the two related samples test. *P* values <.05 were regarded as statistically significant.

RESULTS

Fourteen patients (six women and eight men) were enrolled in the study. The cases' sociodemographic characteristics are shown in tables 1 and 2.

Depressive disorder was determined in 85.8% of the cases, anxiety disorder in 71.5%, and sleep disorder in 78.6%. Descriptive data for severity of anxiety and depression and sleep disorders according to HAM-D, HAM-A, and PSQI scores are shown in Table 3.

Pre-treatment (pre-test) and post-treatment (post-test) scores were compared using the independent samples t test. The cases' LANSS pain scale scores were 19.00±5.11 pre-treatment and 7.57±4.59 post-treatment, the difference being statistically significant (*P*=.001). Significant differences were observed between pre- and post-test HAM-D, HAM-A, PSQI, quality of life (QoL) general health, QoL physical health, or QoL psychological health scores (*P*=.002, *P*=.014, *P*=.002, *P*=.002, *P*=.002, and *P*=.001, respectively). However, no significant differences were determined between pre- and post-test QoL social relationships or QoL environmental health scores (*P*=.160 and *P*=.831, respectively). **(Table 4)**

DISCUSSION

This prospective study examined whether there would be any changes in sleep, quality of life or anxiety and depressive symptoms after SCS treatment in patients with chronic pain. A statistically significant difference in mean LANSS Pain Scale scores was observed after SCS. This finding suggests that there was a significant reduction in pain following SCS administration. In addition, there was a significant decrease in the PSQI scores of the patients after SCS (*P*=.002), indicating a significant improvement in sleep quality. Several studies have shown that pain has a detrimental effect on sleep quality. Özdemir et al. examined 62 patients with pain in their retrospective study and reported that 51% of them had regularized sleep hours after treatment. [22] It is an expected finding that sleep quality is more positively affected by SCS that reduces or prevents the pain experienced, and our data are consistent with previous literature.

Table 1: Descriptive statistics for demographic quantitative variables

	Minimum	Maximum	Mean ± SD
Age (years)	36	60	45.64 ± 8.23
Duration of disease (years)	2	22	7.64 ± 4.94

Values expressed as mean ± SD, minimum, and maximum

Table 2: Descriptive statistics for demographic qualitative variables

		n	%
Gender	Female	6	42.9
	Male	8	57.1
Marital status	Married	2	14.3
	Single	12	85.7
Education	Elementary	4	28.6
	Secondary	7	50.0
	Higher	3	21.4
Work status	Working	9	64.3
	Not working	5	35.7
Diagnosis	Post laminectomy	10	71.4
	Other	4	28.6
History of surgery	Yes	12	85.7
	No	2	14.3

Data are expressed as numbers and percentages (%)

Table 3: Descriptive statistics for clinical variables

		n	%
Depression	None	2	14.3
	Mild	2	14.3
	Moderate	6	42.9
	Severe	4	28.6
Anxiety	None	4	28.6
	Minor	6	42.9
	Major	4	28.6
Sleep disorder	Not present	3	21.4
	Present	11	78.6

Data are expressed as numbers and percentages (%)

Table 4: A comparison of the groups' pre- and post-treatment scale scores

	Pre-Test (n=14)	Post-Test (n=14)	*P*
LANSS pain scale	19.00±5.11	7.57±4.59	**.001***
HAM-D	21.29±10.62	12.14 ±5.52	**.002***
HAM-A	13.57±13.00	10.64±10.25	**.014***
PSQI	8.93±4.81	4.86±4.45	**.002***
QoL-general health	34.8±17.09	66.96±15.20	**.002***
QoL-physical health	37.01±20.65	64.28±12.21	**.002***
QoL-psychological health	69.04±10.93	86.60±8.36	**.001***
QoL-social relationships	67.26±23.22	70.23±23.28	.160
QoL-environmental health	72.10±16.15	72.10±17.31	.831

Independent Two Samples t Test, LANSS: Leeds Assessment of Neuropathic Symptoms and Sign, HAM-D: Hamilton Depression Rating Scale, HAM-A: Hamilton Anxiety Rating Scale, PSQI: Pittsburgh Sleep Quality Index, QoL: Quality of Life

Anxiety and depression are more common and clinically significant in patients with chronic pain than in healthy individuals. In patients with chronic pain, both the pain itself and the presence of difficulties that affect quality of life lead to the emergence of a depressed mood and anxiety. This relationship is bidirectional. In other words, pain and decreased quality of life lead to depressive symptoms, and the presence of depressive symptoms increases the perception of pain and impairs quality of life. Effective treatment of chronic pain reduces both anxiety and depressive symptoms and is also important in improving quality of life. [23] Anxiety also plays an important role in acute pain, as fear of pain and/or anticipatory anxiety may lead to a more pronounced pain perception. However, anxiety symptoms can rapidly decrease with successful pain management. Changes in monoamine neurotransmitters, including serotonin, dopamine and norepinephrine, are involved in both chronic pain and depression. Clinical studies have reported that chronic pain often triggers depression as a result of the stressful situation the individual is in and the prevalence of depression in patients with chronic pain is 85%. [24] In the presence of depression caused by chronic pain, the prognosis is worse than in patients with only chronic pain without depression. There is a close connection between chronic pain and depression in terms of emergence and development, and the two exacerbate each other. This leads to difficulties in the treatment of chronic pain accompanied by depression. [25] Corallo et al. reported that patients with chronic pain had high anxiety and depressive symptoms and significant improvement was observed when pain was reduced. [26] Similarly, in this study, we observed a significant improvement in anxiety and depression scores after SCS compared to pre-treatment values. In addition, another study emphasized the relationship between SCS failure and the presence of psychiatric disorders such as PTSD, depression and anxiety. [27] In this study, we could not record a case without a reduction in pain levels after SCS treatment. Therefore, we could not evaluate failed SCS.

Quality of life is severely impaired in patients with chronic pain. [28] Reducing discomfort in patients with chronic pain or improving impaired quality of life is another important objective of treatment. Significant decreases, indicating improvement, were observed in the QoL general health, physical health, and psychological domain scores post-treatment compared to pre-treatment in this study. Mekhail et al. examined quality of life in SCS outcomes and reported marked clinical and significant improvement in both physical and emotional functioning and in sleep quality. [29] Similar results have been observed in other studies. [30] However, we determined no significant difference between pre- and post-treatment QoL social relationships or QoL environmental health domains. One reason for this may be that they include factors that may be partially independent of the individual, although another reason may be that we only observed the cases for one month. Positive changes may probably be observed in the QoL social relationships and environmental health domains with longer follow-ups, such as for six months or one year.

One of the limitations of our study is that the patients' previous treatments before scs treatment could not be followed up and the patients could not be standardized in this respect. Another limitation is that the patients were followed up for 1 month in our study. It is possible that the data may differ with longer follow-up periods such as 6 months or 1 year.

In conclusion, this study the application of SCS not only effectively reduced pain in treatment-resistant chronic pain, but also mediated significant improvements in sleep quality, anxiety, and depressive states. These data shed useful light on the effects of chronic pain and effective pain management on sleep, anxiety, depression and quality of life and should be considered a preliminary study. More detailed information will be available with longer follow-up studies involving larger populations.

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Evaluation of Volume Controlled Ventilation Mode and Volume Guaranteed Pressure Controlled Ventilation Modes in Lateral Decubitus Position; Randomized Controlled Study

Lateral Dekübit Pozisyonda Hacim Kontrollü Ventilasyon Modu ve Hacim Garantili Basınç Kontrollü Ventilasyon Modlarının Değerlendirilmesi; Randomize Kontrollü Çalışma

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ABSTRACT

Objectives: This study aims to examine the impact of two ventilation modes—volume-controlled ventilation (VCV) and volume-guaranteed pressure-controlled ventilation (PCV-VG)—on patient hemodynamic, lung mechanics, and alveolar gas exchange during laparoscopic surgery in the lateral decubitus position under general anaesthesia.

Methods: The study included 60 patients, aged 18-65, classified as ASA I-II, who were scheduled for laparoscopic nephrectomy. Patients were randomly assigned to either the VCV or PCV-VG group. Parameters such as peak pressure (Ppeak), mean pressure (Pmean), PaO2, PaCO2, SaO2, and haematocrit (htc) were recorded at four time points: in the supine position before lateral decubitus (T1), 5 minutes after lateral decubitus (T2), at the end of surgery in lateral decubitus (T3), and in the supine position before extubation (T4). Additional data collected included patient demographics, surgery details, operation time, and the side of the operation.

Results: When ventilation parameters and blood gas values at T1, T2, T3 and T4 were evaluated, significant differences were seen between the groups in Ppeak at T2 and Pmean at T3 (P<.05). There was no significant difference in PaO2, SaO2 and PaCO2 values between the groups (P>.05). There was a significant difference in Ppeak, Pmean, htc, systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse parameters between the groups at different time periods (P<.05). There was no significant difference in other parameters (P<.05).

Conclusions: Different ventilation modes have unique benefits for different clinical situations. While PCV-VG mode provided a significant decrease in pressure parameters, no difference was observed in blood gas parameters.

Keywords: General Anaesthesia, laparoscopic nephrectomy, lateral decubitus position, ventilation

ÖZ

Amaç: Bu çalışmanın amacı, Genel anestezi altında lateral dekübit pozisyonda iki ventilasyon modunun (hacim kontrollü ventilasyon (VCV) ve hacim garantili basınç kontrollü ventilasyon (PCV-VG)) laparoskopik sırasında hasta hemodinamikleri, akciğer mekaniği ve alveoler gaz değişimi üzerindeki etkisini incelemeyi amaçlamaktadır.

Yöntemler: Çalışmaya laparoskopik nefrektomi planlanan, ASA I-II olarak sınıflandırılan, 18-65 yaş arası 60 hasta dâhil edildi. Hastalar rastgele VCV veya PCV-VG grubuna ayrıldı. Hastaların demografik özellikleri, ameliyat ayrıntıları, ameliyat süresi ve ameliyatın tarafı ve tepe basıncı (Ppeak), ortalama basınç (Pmean), PaO_2, $PaCO_2$, SaO_2 ve hematokrit (htc) gibi yanal dekübitten önce sırtüstü pozisyonda (T1), yanal dekübitten 5 dakika sonra (T1) T2), ameliyat sonunda lateral dekübitte (T3) ve ekstübasyon öncesi sırtüstü pozisyonda (T4) olmak üzere parametreler dört zaman noktasında kaydedildi.

Bulgular: T1, T2, T3 ve T4'teki ventilasyon parametreleri ve kan gazı değerleri değerlendirildiğinde, gruplar arasında T2'de Ppeak ve T3'te ki Pmean'de anlamlı farklılıklar görüldü (P<.05). Gruplar arasında PaO_2, SaO_2 ve $PaCO_2$ değerlerinde anlamlı fark görülmedi (P>,05). Gruplar içerisinde farklı zaman dilimlerinde Ppeak, Pmean, htc, sistolik kan basıncı (SBP), diastolik kan basıncı (DBP) ve nabız parametrelerinde anlamlı fark mevcuttu (P<.05). Diğer parametrelerde anlamlı farklılık yoktu (P<,05).

Sonuç: Farklı ventilasyon modlarının farklı klinik durumlar için benzersiz faydaları vardır. PCV-VG modu basınç parametrelerinde anlamlı düşüş sağlarken kan gazı parametrelerinde farklılık gözlenmedi.

Anahtar Kelimeler: Genel anestezi, laparoskopik nefrektomi, lateral dekübit pozisyon, ventilasyon

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INTRODUCTION

The position of the patients and the ventilation management applied during the surgery may cause some changes in vital parameters. The goal of ideal ventilation is to protect the lungs and provide acceptable gas exchanges. Laparoscopic surgery is widely used in the treatment of various intra-abdominal and retroperitoneal pathologies using minimally invasive approaches. Laparoscopic nephrectomy is a minimally invasive approach frequently used in the surgical treatment of kidney cancer, obstructive uropathy and other kidney diseases. As with every surgical procedure, laparoscopic nephrectomy in the lateral decubitus position has some disadvantages and possible complications. Cardiovascular and respiratory complications may develop due to carbon dioxide insufflation. In addition, it provides benefits such as less postoperative pain, shorter hospital stay, significant reduction in blood loss, faster recovery, and nephron-sparing surgery. During laparoscopic surgery, pneumoperitoneum is created by injecting carbon dioxide (CO_2) into the abdominal cavity. Pneumoperitoneum pushes the diaphragm upward, causing compression at the bases of the lung. Elevation of the diaphragm and increased abdominal pressure leads to a decrease in FRC. Decreased lung volume and pressure on respiratory muscles increase respiratory workload. [1]

Laparoscopic nephrectomy in the lateral decubitus position is an effective and safe method in the treatment of kidney diseases. However, this position may have negative effects on lung dynamics. This can lead to V/Q imbalance. Ventilation-perfusion imbalance and decreased lung volumes can lead to decreased arterial oxygenation. [2] Compression of the underlying lung and reduced ventilation may increase the risk of atelectasis. The upper lung may expand further under the influence of gravity, leading to hyperinflation in the upper lobes.

Volume Controlled Ventilation (VCV) ensures that a certain tidal volume (TV) is delivered to the patient. In this mode, the ventilator delivers a preset volume to the patient during each respiratory cycle. Providing a reliable tidal volume facilitates ventilation control. However, if the patient has low lung compliance, there is a risk of high peak pressures. This may cause barotrauma in the lungs and cause changes in pulmonary gas distribution. [3]

Pressure Controlled Ventilation - Volume Guaranteed (PCV-VG) is a ventilation mode that combines the features of VCV and Pressure Controlled Ventilation (PCV) modes. In this mode, the ventilator guarantees a certain tidal volume while at the same time adjusting the inspiratory pressure, providing a pressure profile appropriate to the patient's lung compliance. Minimizes lung damage thanks to pressure control while providing a reliable tidal volume. [4] Additionally, it provides more physiological respiratory support as it dynamically adapts to the patient's lung compliance.

In this study, we aimed to determine the effect of volume-controlled ventilation mode and volume-guaranteed pressure-controlled ventilation modes on differences in patient hemodynamic, lung mechanics and alveolar gas exchange parameters in patients who underwent laparoscopic surgery in the lateral decubitus position under general anaesthesia.

METHODS

We obtained institutional review board permission from Atatürk University for this study (Date: 29/09/2022 Decision No: 2022/609). This randomized controlled study was conducted on patients who underwent laparoscopic nephrectomy surgery in the lateral decubitus position by the urology clinic at Atatürk University Anaesthesiology and Reanimation Department operating room. Written consent was obtained from all patients participating in the study.

After ethics committee approval was obtained, 60 patients in the ASA I-II group, between the ages of 18-65, without liver, kidney or advanced heart failure, without respiratory system disease, and non-smokers who agreed to participate in the study were included in the study. Patients with underlying serious cardiovascular disease, respiratory system disease, and patients who did not want to participate in the study were excluded from the study.

Anaesthesia induction was applied to the patients with 2-3 mg/kg propofol, 0.7 mg/kg rocuronium, 1 mg/kg fentanyl, and endotracheal intubation was performed when the TOF value was higher than 90%. After endotracheal intubation was performed, ventilation was started with VCV or PCV-VG ventilation mode in accordance with randomization. Arterial catheterization was performed. Ventilation settings were made so that the patients' tidal volume was 8 ml/kg, respiratory rate, end-tidal carbon dioxide levels were 35-40 mmHg, 2 litres of 50% oxygen mixture, I: E ratio was 1:2, and anaesthesia was maintained with desflurane. Ppeak, Pmean, PaO2, PaCO2, SaO2, pH in the supine position before the patient is placed in the lateral decubitus position (T1), in the 5th minute in the lateral decubitus position (T2), in the lateral decubitus position at the end of the surgery (T3), and in the supine position before extubation (T4), haematocrit, SBP, DBP, pulse values

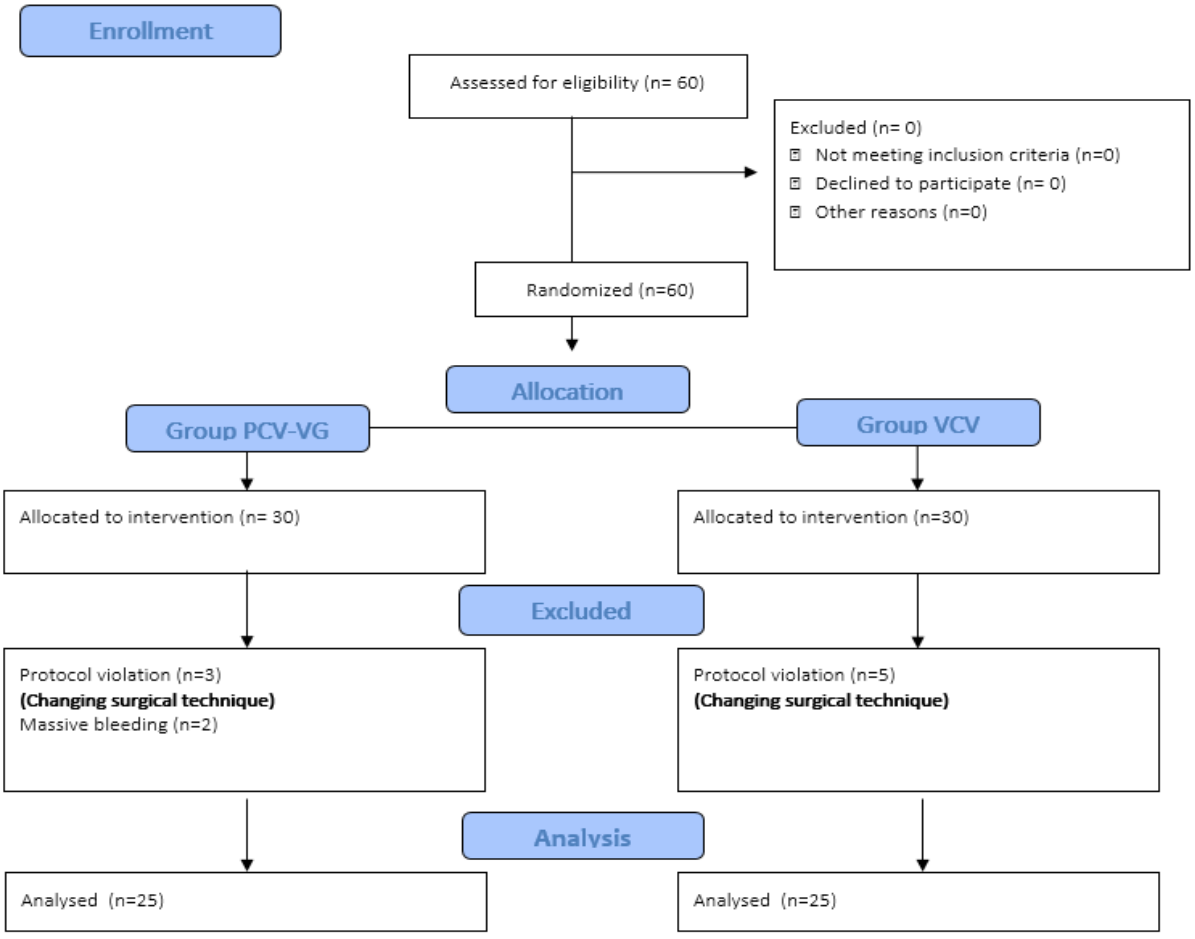
were noted. Demographic data of the patients, surgery, operation time, and the side where the operation was performed were noted. The enrolment and allocation of patients are summarised in a CONSORT flow diagram. (Figure 1)

Statistical analysis

In the post hoc power analysis analysed with the Ppeak parameter in the T2 time unit, the power of the study with a total of 50 patients, 25 patients in each group, was found to be 0.97 (Effect power; 1.04, Type 1 error; 0.05). With this result, it was seen that the sample size was sufficient.

Statistical analysis was performed using the statistical program SPSS (IBM SPSS Corp., Armonk, NY,). Chi-square test was used to evaluate categorical data. The distribution of the data was evaluated with the Kolmogorov-Smirnov test. Student-t test was used between independent groups for data showing normal distribution, and Repeated measures ANOVA test was used for evaluations between different time units. Data obtained at $P<.05$ were considered statistically significant.

Figure 1: Consort diagram



RESULTS

A total of 60 patients, 30 from each group, who underwent laparoscopic nephrectomy in the urology operating room were included in the study. As a result of the study, 5 patients in the VCV group who were converted to laparotomy surgery, 3 patients in the PCV-VG group due to conversion to laparotomy surgery, and 2 patients due to

massive haemorrhage were excluded from the study. There was no statistically significant difference between the groups included in our study in terms of gender, average age, average height, average weight, operation and anaesthesia duration. (*P*>.05) As a result of the evaluation of the ventilation parameters and blood gas values of the patients in the supine position after endotracheal intubation (T1), at the 5th minute in the lateral decubitus position (T2), after the end of the surgery in the lateral decubitus position (T2), and in the supine position before extubation (T4), the Ppeak parameter was measured in the T2 time unit. There was a statistically significant difference between the groups in the T3 time unit and Pmean parameter. (*P*<.05). There was no significant difference in PaO2, PaCO2, SaO2, Htc, SBP, DBP, Pulse values between the groups. (*P*>.05)

Ppeak value was found to be higher in the VCV group than in the PCV-VG group at T2 time (*P*<.05). There was no significant difference at T1, T3, T4 times (*P*>.05).

Pmean value was found to be higher in the PCV-VG group than the VCV group at T3 time (*P*<.05). There was no significant difference at T1, T2, T4 times (*P*>.05).

When different times are evaluated in the same group, in the VCV group; Ppeak was found to be higher at T2 time than T1 (*P*<.05). T3 was found to be lower than T2 (*P*<.05). T4 was found to be lower than T3 and T2 (*P*<.05). Pmean was found to be higher in T2 than in T1 (*P*<.05). Htc T2 is lower than T1; T3 was found to be lower than T2 and T1, and T4 was found to be lower than T1 (*P*<.05). SBP lower than T2, T1, higher than T4, T2 and T3 (*P*<.05), DBP lower than T2, T1, higher than T4, T1 (*P*<.05), Pulse; T2 was lower than T1; T3 was lower than T1; T4 was higher than T3 (*P*<.05).

When different times were evaluated in the same group, Ppeak T2 was found to be higher than T1 in the PCV-VG group (*P*<.05). T3 was found to be higher than T1 (*P*<.05). T4 was found to be lower than T3 and T2 (*P*<.05). Pmean T2 was higher than T1, T3 was higher than T1, T4 was lower than T2 and T3 (*P*<.05). Htc T2 was found to be lower than T1, T3 was lower than T1, and T4 was lower than T1 and T2 (*P*<.05). SBP, T4 was higher than T2 and T3 (*P*<.05), in DBP, T2 was lower than T1, T3 was lower than T1, T4 was higher than T2 and T3 (*P*<.05), Pulse T2 was higher than T3 and T4 was lower than T1 (*P*<.05).

There was no statistically significant difference in PaO2, PaCO2, SaO2 parameters in the same group at different times. (*P*>.05)

DISCUSSION

Laparoscopic surgery in the lateral decubitus position has significant effects on lung dynamics. These effects may become more pronounced with pneumoperitoneum and may lead to complications such as ventilation-perfusion imbalance, atelectasis, and reduced oxygenation. Therefore, it is of great importance to take appropriate precautions and optimize ventilation strategies. The selection of VCV and PCV-VG modes varies depending on the patient's clinical condition and lung dynamics. Situations where the VCV mode is preferred include situations where a stable tidal volume requirement and ventilation control are at the forefront. PCV-VG mode is preferred especially in patients with variable lung compliance, in order to reduce the risk of barotrauma and provide more physiological ventilation.

In our study, we compared the effects of PCV-VG and VCV ventilation modes on lung parameters and hemodynamic in patients who underwent laparoscopic nephrectomy surgery in the lateral decubitus position. As far as can be determined, this is the first study comparing ventilation modes in laparoscopic cases in the lateral decubitus position. When the patients were moved from the supine position to the lateral decubitus position, the Ppeak value was observed to be lower in the PCV-VG mode. When their time periods were compared, it was seen that both groups reached the highest value in the lateral decubitus position. However, there was no significant difference in arterial oxygenation, which was similar to previous studies5. Many previous studies have found that the Ppeak value is lower in the PCV-VG mode than in the VCV mode. Dion et al. found that Ppeak pressures were lower in mechanical ventilation modes compared to pressure control modes in patients undergoing laparoscopic sleeve gastrectomy surgery. [5]

Pmean value related to alveolar ventilation and oxygenation was significantly higher in the PCV-VG group in the lateral decubitus position. Pmean is related to alveolar pressure, and an increased Pmean can stimulate the alveoli, improving alveolar ventilation and gas oxygenation. [6] However, in our study, although the Pmean value was significant at T3 time, no significant difference was found between the two groups in arterial oxygenation at any time. A meta-analysis by Aldenkortt et al evaluated 13 studies involving various ventilation strategies in obese adults. Similar to our study, they concluded that neither VCV nor PCV modes were superior for improving oxygenation or ventilation in patients. [7] In a study conducted on patients in the supine position who underwent VCV and PCV-VG, a significant decrease in Ppeak pressures was found, similar to our study. This decrease in Ppeak pressures was observed

to be accompanied by a significant increase in compliance values. This result appears to be due to the generation of similar tidal volumes with lower airway pressures. Similar to our study, the authors concluded that PCV-VG may result in less airway damage in patients with high airway pressure values. [8]

Tablo 1: Comparison of Demographic Variables Between Groups

	VCV (n:25)	PCV-VG (n:25)	*P*
Age	49.3 ± 11	53.08 ± 12.4	.258
Weight	82.4 ± 13.5	80.36 ± 15.3	.619
Height	171.2 ± 6.9	169.92 ±10.2	.616
Gender (F/M)	9/16	10/15	N
Duration of the surgery	164.4 ± 46.2	172.7 ± 47.5	.538
Duraiton of the Anesthesia	194.4 ± 46.7	207.1 ± 50.7	.361
Comorbidities (Y/N)	8/17	12/13	.357
Side of the surgery (Right/Left)	12/13	13/12	N

Datas expressed with mean±SD and number

Table 2: Descriptive statistics for demographic qualitative variables

		T1	T2	T3	T4	*P*
Ppeak	VCV	17.68±2.49	21.08±2.51[a]	19.64±3.37[a.b]	17.60±3.73[b.c]	**<.001**
	PCV-VG	15.64±2.95	18.08±3.17[a]	17.88±3.34[a]	16.36±2.81[b.c]	**<.001**
	P	.11	**.001**	.070	.191	
Pmean	VCV	8.64±1.07	9.60±1.47[a]	9.08±1.18	8.80±1.63	**.024**
	PCV-VG	8.92±1.35	10.00±1.32[a]	9.92±1.46[a]	8.84±1.90[b.c]	**.001**
	P	.422	.317	**.031**	.937	
PaO_2	VCV	135.55±33.07	137.80±27.19	148.13±30.28	144.46±33.60	.262
	PCV-VG	145.24±25.62	143.74±28.05	143.15±27.26	137.61±26.24	.376
	P	.253	.451	.544	.426	
$PaCO_2$	VCV	36.72±4.72	34.94±4.73[a]	36.74±4.59[a.b]	36.89±4.26[c]	.092
	PCV-VG	34.78±3.15	33.59±3.42[a]	36.69±4.52[b]	37.19±4.23[c]	.092
	P	.095	.254	.968	.804	
SaO_2	VCV	97.90±1.91	98.12±1.89	98.39±1.38	98.12±1.50	.521
	PCV-VG	98.66±1.05	98.43±1.35	98.29±1.72	98.28±1.16	.476
	P	.902	.506	.822	.692	
Htc	VCV	43.33±7.33	42.09±6.93[a]	40.54±6.26[a.b]	40.47±6.94[a]	**.002**
	PCV-VG	42.90±4.77	41.06±5.79[a]	39.11±4.26[a]	39.00±5.04[a.b]	**<.001**
	P	.806	.571	.350	.397	
SBP	VCV	124.12±20.83	109.64±20.46[a]	114.68±20.42	122.44±23.81[b.c]	**.019**
	PCV-VG	119.32±21.19	112.24±21.63	110.64±19.09	125.96±22.64[b.c]	**.012**
	P	.423	.664	.474	.595	
DBP	VCV	73.40±11.86	65.24±11.73[a]	67.84±12.84	71.60±13.98[b]	**.020**
	PCV-VG	73.08±13.84	65.52±10.82[a]	64.72±12.26[a]	72.96±14.59[b.c]	**.008**
	P	.930	.930	.384	.738	
Nabız	VCV	80.48±14.55	76.00±19.18[a]	70.80±12.54[a]	79.32±15.20[c]	**.013**
	PCV-VG	83.20±12.77	75.88±11.66[a]	75.04±10.55[a]	77.20±15.22[a]	**.008**
	P	.486	.979	.202	.625	

Data expressed with mean±SD, PaO2; Partial oxygen pressure, PaCO2; Partial carbon dioxide pressure, SaO2; Oxygen saturation, Htc; hematocrit, SBP; systolic blood pressure, DBP; diastolic blood pressure.

[a] Significant difference between T1 and other time intervals.

[b] Significant difference between T2 and other time intervals

[c] Significant difference between T3 and other time intervals

The lack of significant difference in hemodynamic parameters such as SBP, DBP, and pulse was similar to previous studies. In a meta-analysis study by Han et al., which included randomized controlled studies, it was shown that there was no significant difference between groups in hemodynamic parameters, similar to our study. [8-9] The omission of the recruitment manoeuvres can be considered a limitation of the study.

CONCLUSION

VCV and PCV-VG are two important modes of mechanical ventilation, each offering advantages for specific clinical situations. While VCV is a simple mode that guarantees constant volume, PCV-VG is a more complex but potentially safer option with pressure limitation and the ability to adapt to dynamic fit. Clinical results vary depending on the individual patient's condition, respiratory mechanics and hemodynamic stability. Therefore, a patient-specific ventilation strategy should be developed, taking into account the advantages and disadvantages of both modes.

Ethics Committee Approval: Ethics committee approval was obtained from Atatürk University Local Ethics Committee (Date: 29.09.2022, Number: 2022/609))
Informed Consent: Patient consent form was achieved.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept- **ECÇ, ENMK**; Design- **ECÇ, ENMK,VK**; Supervision- **ECÇ, ENMK**; Resources- **VK,KG**; Data Collection and/or Processing- **ENMK,VK,KG**; Analysis and/or Interpretation- **ECÇ, ENMK**; Literature Search- **ENMK**; Writing Manuscript- **ENMK**; Critical Review- **ECÇ**;
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Etik kurul onayı Atatürk Üniversitesi Yerel Etik Kurul Başkanlığı'ndan (Tarih:29.09.2022, Sayı:2022/609) alınmıştır.
Hasta Onamı: Tüm hastalardan aydınlatılmış hasta onamı alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir- **ECÇ, ENMK**; Tasarım- **ECÇ, ENMK,VK**; Denetleme- **ECÇ, ENMK**; Kaynaklar- **VK,KG**; Veri Toplanması ve/veya İşlemesi- **ENMK,VK,KG**; Analiz ve/ veya Yorum- **ECÇ, ENMK**; Literatür Taraması- **ENMK**; Yazıyı Yazan- **ENMK**; Eleştirel İnceleme- **ECÇ**;
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

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Research Article *Araştırma Makalesi* DOI: 10.61745/ jsmsau.1517053

Olfactory Bulb Lesion Induced Pineal Gland Calcification: a First Experimental Study

Olfaktör Bulbus Lezyonu ile İndüklenmiş Pineal Gland Kalsifikasyonu: İlk Deneysel Çalışma

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ABSTRACT

Objectives: There is no enough stereological study that seriously mentions maternal olfactory disorders among the causes of pineal gland insults. This study sought to examine the connection between lesions caused by olfactory bulbectomy and changes in the pineal gland in rats
Methods: A total of 24 male rats were used in the experiment, 5 control, 6 SHAM and 13 study. After a 1 mm burrhole was opened in the midfrontal-interpupillary line for the subjects in the SHAM and study groups, only the olfactory dura was opened in the SHAM group, while the olfactory bulbs were crushed in study group. They were sacrificed after a two-month follow-up. The number of calcified pineal cells (n/mm^3) determined. Results analyzed with the Mann-Witney U test.
Results: The mean calcified pineal cells numbers (n/mm^3) were measured as per cubic milimeters as: (7±2) x10^3/mm^3) in control (Group I); (15±3) x10^3 in SHAM (Group II); (34±9) x10^3 in study group (Group III). *P*<.005/(GI-GII); *P*<.0005/(GII-GIII); *P*<.00001/(GI-GIII).
Conclusions: Olfactory bulb lesion may be responsible for pineal gland calcification. Pathologies in the pineal gland resulting from olfactory bulbectomy may contribute to various endocrine, immune, and reproductive disorders with unclear etiologies.

Keywords: Olfactory bulb lesion, pineal gland, calcification

ÖZ

Amaç: Pineal bez hastalıklarının nedenleri arasında maternal koku bozukluklarından ciddi şekilde bahseden yeterli stereolojik çalışma bulunmamaktadır. Bu çalışma, olfaktör bulbektominin neden olduğu lezyonlar ile sıçanlarda pineal bezdeki değişiklikler arasındaki bağlantıyı incelemeyi amaçlamıştır.
Yöntem: Bu çalışmada 5 kontrol, 6 Sham ve 13 çalışma olmak üzere toplam 24 erkek sıçan kullanıldı. Sham ve çalışma grupları için midfrontal-interpupiller çizgide 1 mm'lik bir burrhole açıldıktan sonra, Sham grubunda sadece olfaktor dura açıldı, çalışma grubunda ise olfaktor bulbuslar hasarlandırılmıştır. İki aylık takipten sonra sıçanlar öldürüldüler. Kalsifiye edilmiş pineal hücre sayısı (n/mm3) belirlendi. Sonuçlar Mann-Witney U testi ile analiz edildi.
Bulgular: Ortalama kalsifiye pineal hücre sayısı (n/mm^3) milimetre küp başına şu şekilde ölçüldü: Kontrolde (Grup I) (7±2) x10^3/mm^3); SHAM'da (Grup II) (15±3) x10^3); (34±9) x10^3 çalışma grubunda (Grup III). *P*<.005/(GI-GII); *P*<.0005/(GII-GIII); *P*<.00001/(GI-GIII).
Sonuç: Olfaktör bulbus lezyonu pineal bez kalsifikasyonundan sorumlu olabilir. Olfaktor bulbektomi sonucu pineal bezde oluşan patolojiler etiyolojisi tam olarak bilinmeyen çeşitli endokrin, immün ve üreme bozukluklarına yol açabilir.

Anahtar Kelimeler: Olfaktör bulbus lezyonu, pineal bez, kalsifikasyon

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INTRODUCTION

The pineal gland, a small endocrine structure situated in the midline of the brain above the thalamus, plays a crucial role in regulating circadian rhythms through the secretion of melatonin. Postnatally, the number of pineal gland cells increases progressively. [1] While a direct anatomical or functional link between the pineal gland and olfactory nerves has not been fully established, studies suggest that peripubertal olfactory bulbectomy may lead to pineal gland degeneration, a reduction in pinealocyte numbers, hypothalamo-hypophyseal disruptions, loss of prolactin-secreting cells, and abnormalities in prolactin secretion. Histopathological changes, including calcification of the pineal gland, have also been observed following olfactory or light deprivation. The olfacto-pineal pathways are implicated in the modulation of feeding, reproductive, and sexual behaviours. [2–7] The olfato-pineal pathways are crucial in the modulation of feeding, reproductive and sexual behaviour.

METHODS

Ethics committee approval was obtained from Ethics Committee for Animal Experiments, Medical Faculty, Ataturk University of Turkey (Date: 09.011.2022, Number: 2200369071). The study involved 24 female rats, divided into three groups: 5 controls, 6 SHAMs, and 13 in the experimental group. The rats were housed individually in metal cages at room temperature, maintained under a 12-hour light cycle with 50% relative humidity, and monitored by a veterinarian. They were provided with standard laboratory feed and water ad libitum. The study design and permissions received approval from the Ethics Committee for Animal Experiments at the Medical Faculty of Atatürk University, Turkey. The care and experimental procedures adhered strictly to the guidelines established by this ethics committee.

Under general anaesthesia, after opening a 1mm burrhole on the midfrontal-interpupillary line for SHAM and the subjects in the study group, the dura covering only the olfactory bulbs was incised, and the olfactory bulbs in the study group were additionally injured with a clamp. After 1 month, the subjects were taken to their cages and lived with fertile male rats for 2 months. After the 2-month follow-up of the new-born pups, Sacrification was performed following the intracardiac formalin injection under inhalation anaesthesia and they were dehydrated in 10% formalin solution in groups.

Histopathological Procedures

The olfactory nerves were removed along with the entire brain and fixed in a horizontal position, and 20 consecutive sections were taken at 10 micron intervals for glomerulus and olfactory fila examination. The same procedures were performed for the pineal gland. Preparations were stained with hematoxylin-eosin and Calcium Stains (Von Kossa Calcium Set). Olfactory nerve volumes were estimated using ellipsoid volume formulas and calcified cell numbers were estimated stereologically.

Stereological analysis

Sampling of 30 consecutive sections of 5 micrometres taken from the pineal gland and calcified cell density (n/mm^3) were analysed using the physical dissector method.

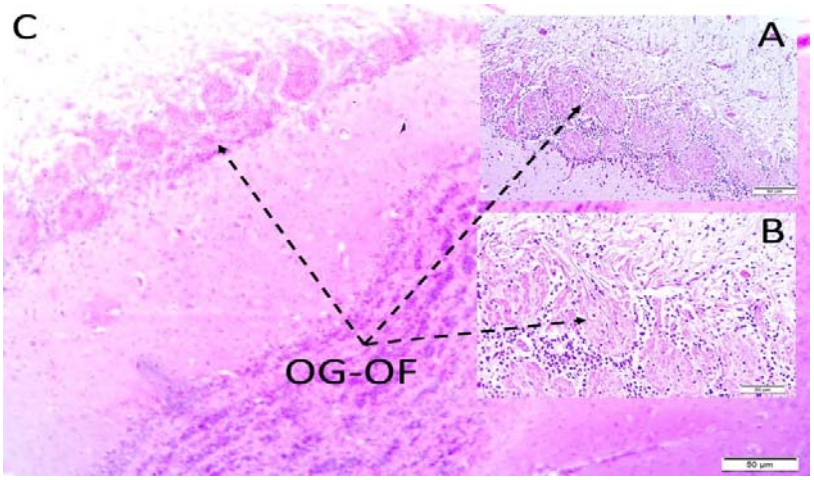

Figure-1: Normal olfactory glomeruli and normal ciliary processes (olfactory fila) were observed in the normal subject, while slightly small and atrophic olfactory glomeruli and reduced olfactory fila (OG-OF) were observed in the SHAM group, and severely atrophic olfactory glomeruli and greatly reduced olfactory fila were observed in the study group (LM, H&E, x20).

RESULTS

Clinical results: One animal in the study group (n=1) dead died within the seven days of surgery and they were changed new one. Neck stiffness, unconsciousness, convulsive attacks, fever, apnea, cardiac arrhythmia, and breathing disturbances were observed in animals. Two animals in the study group (n=2) and one animal in the SHAM group (n=1) were died within the seven days of surgery and they were switched with new ones. Neck stiffness, unconsciousness, convulsive attacks, fever, apnea, cardiac arrhythmia, and breathing disturbances were reported in dead animals. In control animals, the heart rate was 289±16/min, the respiratory rate was 32±6/min and the blood oxygen concentration was 93±7(%). OBX applied animals shown anosmia, memory loss.

Numerical results: The mean calcified pineal cells numbers (n/mm^3) were measured as per cubic millimetres as: (7±2)x10^3/mm^3) in control (Group I); (15±3)x10^3 in SHAM (Group II); (34±9)x10^3 in study group (Group III). *P*<.005/(GI-GII); *P*<.0005/(GII-GIII); *P*<.00001/(GI-GIII).

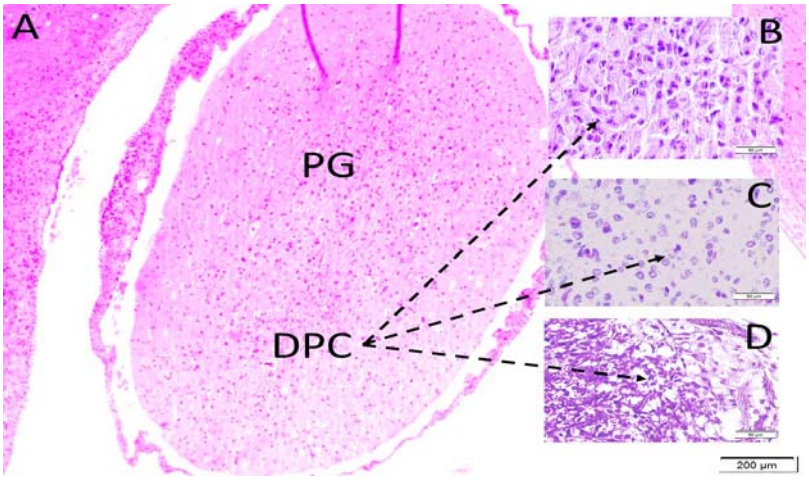

Figure-2: Normal pineal gland, normal and normal pineal cells are observed in the normal subject, slightly small, degenerated and atrophic pineal cells (DPC) in the SHAM group, and highly atrophic small and degenerated atrophic cells (DPC) in the study group (LM, H&E, x4/A; x20/B-D).

DISCUSSION

The number of pineal gland cell nuclei of rat continuously increased during post-natal life and differences between the lactation and after weaning periods were significant. It is possible that the supporting cells, fibres and new synapses are responsible for that PG late post-natal increase. [1] In the winter pineal gland sensitivity is increased. [8] Pineal denervation cause testicular regression. [9] Olfactory bulb lesions cause mammary gland and corpus luteum degeneration. [3,10] There are some indirect antitumor effects of olfactory bulbecrtomy on the suppression of growth of some prostatic tumour strains. [11]

Olfactory bulbectomy resulted in increased morning gonadotropin levels and ovarian weight in animals in reproduction phases in animals on a short photoperiod. [12] Olfactory bulbectomy leads to hypothalamo-hypohiseal insults in lactating animals. [4] The pineal gland causes mammotroph hypotrophy and hypoplasia in blind-anosmic female rats. [13] Olfactory bulbectomy prevents the testicular regression with the antigonadotropic effect of melatonin. [14] Olfactory bulbectomy have antigonadal actions. [15] Pineal inhibits prolactin synthesis, storage and release in both female and male blind-anosmic rats. [5] There is inhibitory effect of the pineal gland on the prolactin synthesis cells of blind-anosmic female rats following olfactory bulbectomy. [6] Photoperiodic control can be loss oin reproduction time in olfactory-bulbectomized rats. [2] Anosmic rats shows prolactin secretion abnormalities. [13] Anosmic male rats have an increased sensitivity to antigonadotrophic and prolactin -inhibitory effects of melatonin. [16] Olfactory deprivations have antigonadal actions. [15] Pubertal prolactin cell development inhibited in anosmic female rats. [17] Olfactory bulbectomy seems to be responsible for Onuf's nucleus degeneration. [18] Onuf's nucleus degeneration secondary to olfactory bulbectomy seems to be responsible for reduced sperm numbers. [19]

Olfactory bulbectomy may lead to mammary gland degeneration, intestinal immunodeficiency causing by olfaction loss induced denervation injury of Peyer's patches, diminished thyroid hormone secretion and serious behavioral, neurochemical, neuroendocrine, and neuroimmune alterations. [20–23]

Histopathological alterations occur in blind-anosmic female rats. [5] Peripubertal olfactory bulbectomy may lead to pineal gland degeneration. [17] Olfactory bulb lesions cause decreased pinealocyte numbers. [24] Pineal gland may have calcified following olfactory or light deprivation. [7] The pineal gland calcified in the aging rats. [25] Olfaction deficits creating COVID-19 may cause pineal gland dysfunction. [26] So, damage to the olfactory pathways may cause functional cytoarchitectural disorders in the pineal gland.

Limitation: This study does not include biochemical data.

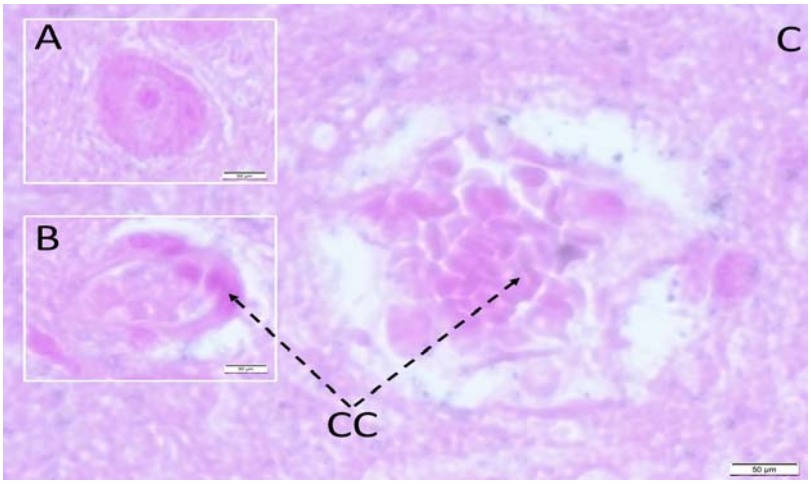

Figure-3: Normal pineal cells are observed in the normal subject, slightly calcified pineal cells in the SHAM group, and highly calcified pineal cells in the study group (LM, H&E, x20).

CONCLUSION

Therefore, various pathologies that cause damage to the olfactory pathways can cause functional histopathological changes in the pineal gland. Chemicals that damage the olfactory nerves should also be avoided.

Future Insights: Olfactory bulbectomy leading pineal gland pathologies may be responsible for many endocrine, immune and reproductive diseases with obscure etiology.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee for Animal Experiments, Medical Faculty, Ataturk University of Turkey (Date: 09.011.2022, Number: 2200369071)
Informed Consent: Our study, for which ethical approval was received, is a cross-sectional study and patient consent is not required.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept - **MKK, MDA** Design- **MKK, MDA**; Supervision- **MKK**; Resources- **MKK**; Data Collection and/or Processing- **MKK, MDA**; Analysis and/or Interpretation- **MKK**; Literature Search- **MKK, MDA**; Writing Manuscript- **MKK**; Critical Review- **MKK**.
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Etik kurul onayı Atatürk Üniversitesi Tıp Fakültesi Deney Hayvanları Etik Kurulu biriminde alınmıştır (Tarih: 09.011.2022, Sayı: 2200369071)
Hasta Onamı: Etik onayı alınan çalışmamız kesitsel bir çalışma olup hasta onamı gerekmemektedir.
Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir- **MKK, MDA**; Tasarım- **MKK,MDA** ; Denetleme- **MKK**; Kaynaklar- **MKK**; Veri Toplanması ve/veya İşlemesi- **MKK, MDA**; Analiz ve/ veya Yorum- **MKK**; Literatür Taraması- **MKK**, **MDA**; Yazıyı Yazan- **MKK**; Eleştirel İnceleme- **MKK**;
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

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ATATÜRK ÜNİVERSİTESİ YAYINLARI ATATURK UNIVERSITY PUBLICATIONS

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The Effect of Local Cold Application after Total Knee Arthroplasty: a Systematic Review

Total Diz Artroplastisi Sonrası Lokal Soğuk Uygulamanın Etkisi: Sistematik İnceleme

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ABSTRACT

Objective: In the present systematic review, it was aimed to review the studies systematically that researched the effect of local cold application after total knee arthroplasty.
Methods: The open-access full-text articles published between 2002-2023 in Turkish and English languages with prospective, randomized controlled experimental and semi-experimental control group design that researched the effects of local cold application on the operation site after total knee arthroplasty were examined to carry out a systematic review. The advanced screening method was applied using Turkish and English equivalents of the keywords ''total knee arthroplasty and cold application'', ''total knee arthroplasty and cold therapy'', ''total knee arthroplasty and cold compress therapy'', ''the effect of cold therapy in total knee arthroplasty'' separately and together in the Pubmed, Google Scholar, ScienceDirect, Cochrane, Turkish Medline, Scopus and Cinahl databases. Totally 2,233 articles were reached. 7 studies which met the sample criteria were included in the systematic review.
Results: In the sample groups of the studies included in the systematic review, it was determined that cold application significantly reduced pain and swelling (P<.05), analgesic drug use (P<.05), bleeding and haemoglobin loss (P<.05), and contributed to faster and more effective ROM exercises in patients with total knee arthroplasty and local cold application.
Conclusion: It was observed that application of cold methods particularly in the early period had a positive effect on pain, swelling, haemorrhage and haemoglobin loss and amount of analgesic use underwent total knee arthroplasty

ÖZ

Amaç: Bu sistematik incelemede, total diz artroplastisi sonrası lokal soğuk uygulamanın etkisini araştıran çalışmaları sistematik olarak incelenmesi amaçlanmıştır.
Yöntemler: Sistematik inceleme amacıyla total diz artroplastisi sonrası ameliyat bölgesine lokal soğuk uygulama yapılarak etkilerinin araştırıldığı, 2002-2023 yılları arasında yayınlanan, yayın dili Türkçe ve İngilizce olan, prospective, randomize kontrollü deneysel ve yarı-deneysel kontrol gruplu tasarım tipinde olan ve tam metin erişimine açık makaleler incelendi. Pubmed, Google Scholar, ScienceDirect, Cochrane, Türk Medline, Scopus ve Cınahl veri tabanlarında ''total diz artroplastisi ve soğuk uygulama'', ''total diz artroplastisi ve soğuk terapi'', ''total diz artroplastisi ve soğuk kompress terapi'', ''total diz artroplastisinde soğuk terapinin etkisi'' anahtar kelimeleri tek tek ve birlikte kullanılarak gelişmiş tarama yöntemi uygulandı. Toplam 2.233 makaleye ulaşıldı. Bu makalelerden örneklem ölçütlerini sağlayan 7 çalışma inceleme kapsamına alınmıştır.
Bulgular: Sistematik inceleme kapsamına alınmış çalışmaların örneklem grubunu total diz artroplastisi geçirmiş ve lokal soğuk uygulama yapılan hastalarda; ağrı ve şişkinliği azalttığı (P<.05), kanama ve hemoglobin kaybını azalttığı (P<.05), ROM hareketlerinin daha hızlı ve etkin yapılmasına katkı sağladığı (P<.05) belirlenmiştir.
Sonuç: Soğuk uygulama yöntemlerinin total diz artroplastisi geçiren hastalara özellikle erken dönemde uygulanmasının hastaların ağrı, şişlik, kanama ve hemoglobin kaybı, analjezik kullanım miktarı, erken mobilize olmaları, taburculuk süresi, hasta memnuniyet oranı üzerinde pozitif bir etkisinin olduğu görülmektedir.

Anahtar Kelimeler: Total diz artroplastisi, cryotherapy, soğuk terapi, lokal soğuk uygulama.

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INTRODUCTION

Total knee arthroplasty (TKA) is a surgical treatment technique applied in serious joint injuries of the knee. Its general indications include osteoarthritis, rheumatoid arthritis, inflammatory polyarthropathies, instability and deformity causing severe pain associated with advanced joint disease unresponsive to conservative treatment. The conditions such as recently suffered septic arthritis and paralysis of the muscles surrounding the related joint and neuropathic joint disease, advanced level osteoporosis and very serious ligament lesion around the joint are evaluated as its contraindications. Urinary retention and urinary infection, delayed wound healing, nerve injuries (particularly peroneal nerve), stress fractures (patella, femur and tibia), instability, subluxation and dislocation of prosthesis, and infection are the potentially developing complications. There is no certain age limit for inflammatory joint diseases such as rheumatoid arthritis, however, age, occupation, daily activity level and most importantly body weight of the patient should be absolutely taken into consideration in planning knee prosthesis for degenerative osteoarthritis. Total knee arthroplasty is performed more frequently between 65-84 years of age and in women. It is usually not preferred in the patients who are below 60 and obese. More simple interventions such as osteotomy should be primarily preferred in the younger patients. The objectives of total knee arthroplasty can be summarized as relief of severe pain, repair of the deformities, retrieval of the functions and prevention or removal of the painful secondary effects. The life quality of the patient is increased by decreasing the pain using this technique. [1-4]

Joint stiffness, limited motion in the knee function, pain, oedema (swelling), haemorrhage and infection are the most common complications after total knee arthroplasty. As well as pharmacological methods such as administration of antibiotics and analgesics, non-pharmacological methods such as cold application, kinesiological banding, elevation, deep friction massage, lower limb exercises, quadriceps femoris isometric exercises and straight leg raising are also used to cope with these complications. [5]

At the present time, cold applications are used as the adjuvant treatment methods in many fields such as particularly orthopaedics and traumatology, rheumatology and neurology. [6] Local cold application was found effective on pain management and functional knee scores in the postoperative period after total knee arthroplasty operations. [7-8]

Local cold application is a low-cost and simple treatment which reduces temperature level of the tissue using ice or cooled water bags on the skin surrounding the injury. [9-10] The kinds of local cold application are cold pack, ice massage, gel packs, immersion packs, cold towel, intermittent cooling equipments and sprays. Local cold application penetrates soft tissues, decreases internal temperature of the joint and consequently decelerates the transmission of the nerve stimuli when applied on a joint. [11-12] These changes reduce both transmission of the harmful signals and also inflammatory response and thereby perceived pain, swelling and blood flow decrease. [13]

The aim of the present systematic review was to systematically examine the effect of local cold application after total knee arthroplasty and contribute to the literature by increasing the awareness on this subject. In this study, the question of "What is the effect of local cold application after total knee arthroplasty?" was explored in accordance with the aim of the study.

METHODS

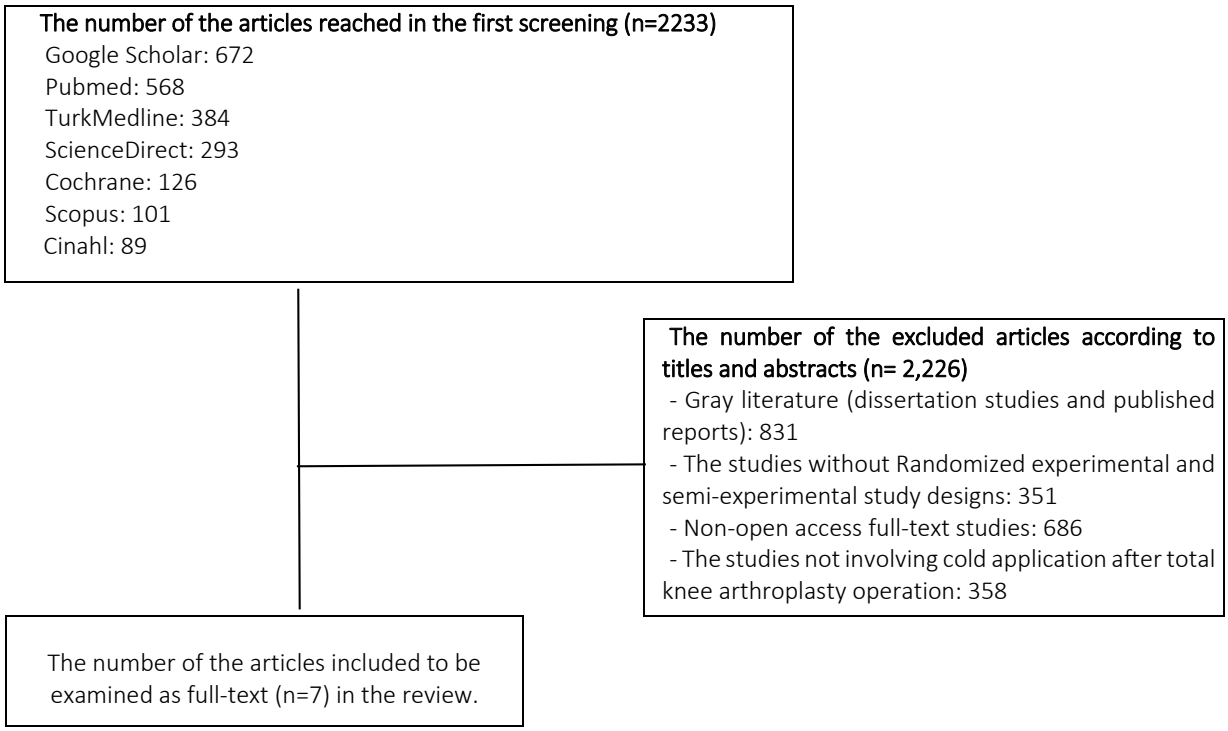
Screening process: Literature screening was carried out using the keywords ‘‘total knee arthroplasty and cold application’’, ‘‘total knee arthroplasty and cold therapy’’, ‘‘total knee arthroplasty and cold compress therapy”, “The effect of cold therapy after total knee arthroplasty’’ and Turkish equivalents of these words. The last screening was performed on 23th June 2023. The research articles related with the subject published between 2002-2023 were involved in the review. As a result of the screening, 672, 568, 384, 293, 126, 101 and 89 studies were reached in the databases of Google Scholar, Pubmed, Turkish Medline, Science Direct, Cochrane, Scopus and Cinahl, respectively. Totally 2,233 studies were reached. The titles and abstracts of these studies were examined by the researchers, evaluated with respect to inclusion criteria of the research and consequently 7 studies were included in the systematic review. In this review, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist tool was used for literature screening, as well as summarizing and reporting the obtained results. (Figure 1) All researchers contributed equally at all stages of this study.

Inclusion criteria: The open-access full-text articles published between 2002-2023 in Turkish and English languages with prospective, randomized controlled experimental and semi-experimental control group designs were included in the systematic review. The present review involved the studies that were published in a national/international peer-review journal and constituted by the patients who received cold-application in the

postoperative period after total knee arthroplasty. Seven studies that met inclusion criteria were enrolled in the review.

Exclusion criteria: As a result of the screening, reports and dissertation studies defined as gray literature, studies without randomized experimental and semi-experimental study designs, non-open access full-text studies and the studies not involving local cold application after total knee arthroplasty operation were excluded from the systematic review.

Figure 1. The flow diagram of literature screening and study selection (PRISMA)- 2009



RESULTS

Li et al. have evaluated pain level, analgesic consumption, haemoglobin values, haemorrhage amount, swelling on the knee, sleep quality and patient satisfaction in their study conducted on totally 389 patients consisting of Control group (n: 192) with a mean age of 61.8±5.8 years who underwent total knee arthroplasty operation between May 2012 and May 2014 and Intervention group (n:197) with a mean age of 60.7±6.5 years. It was encountered that both groups were administered diclofenac sodium (50 mg) parecoxib (40 mg) and tramadol as medication. The Intervention group was additionally administered cold irrigation solution containing 0.5% epinephrine for 30-40 minutes with intervals of 4 hours during the postoperative 24 hours. The Control and Intervention groups were assessed with VAS pain scores in the first 4 hours (*P*= .0016) and at the end of the 24 hours (*P*=.0004). Analgesic consumption: 0-12th hours (*P*=.0033), 12th-24th hours (*P*=.0021). Haemoglobin level: 30.2 g/dl in the Control Group and 26.1 g/dl in the Intervention Group. Haemorrhage amount: 155.8 ml in the Control Group and 130.6 ml in the Intervention group. Swelling on the operation site was assessed as 2.3 cm in the Control group and 1.9 cm in the Intervention group (*P*=.0007). The mean sleep quality was 45.2% in the Control group and 49.6% in the Intervention group (*P*=.01). The patient satisfaction rate was assessed to be 74.8% in the Control group and 76.8% in the Intervention group (*P*=.03). It was reported that the Intervention group had significantly lower pain score compared with the Control group, analgesic consumption decreased, sleep quality increased, haemoglobin and blood loss were lower, swelling on the operation site was significantly lesser and patient satisfaction level was higher than the Control group, therefore, use of cold irrigation

solution containing 0.5% epinephrine was recommended for also its low-cost. [14]

Totally 60 patients, consisting of 27 patients who underwent unicondylar arthroplasty and total knee arthroplasty between 2013-2014 in the Control group and 33 patients in the Intervention group, were evaluated in the study of Kuyucu et al. The mean ages of the Control and Intervention groups were determined as 67.2 (57-78) and 68.4 (53-78) years, respectively. Visual Analog Scale (VAS) scores for pain conditions, Knee Society Scores (KSS) for knee function test, haemorrhage amount and haemoglobin levels were assessed in their study. It was reported that both groups received routine therapy while Intervention group additionally received cold application preoperatively for 2 hours and postoperatively for 1 hour at every 6 hours and 2 hours every day during the following 4 days. VAS Pain score of the Control group was 4.5-3.3 between 1st-5th days whereas VAS Pain score ranged between 2.1-3.0 in the Intervention group (*P*<.05 for all days). The mean knee society function score (KSS): Control group: 80.3; Intervention group: 90.5 (*P*<.05). The mean haemoglobin levels: Control Group: 12.8-9.0 mmol/d, Intervention group: 12,5-9.1 mmol/dl (*P* >.05 for all days). Mean haemorrhage amount: Control Group: Intraoperative haemorrhage: 114 (90-150). Intervention Group: 116 (80-180) (*P*>.05). Postoperative haemorrhage: Control Group: 400.4 cc (140-650). Intervention Group: 365 cc (150-900) (*P*>.05 for all days). It was observed that there was a significant difference between two groups in terms of pain assessment and consequently in terms of analgesic use. It was reported based on the knee society function score that Intervention group had higher range of motion whereas no significant difference was found between the groups regarding haemorrhage amount and haemoglobin values. [15]

Desteli et al. have evaluated totally 87 patients constituted by 45 patients who underwent total knee arthroplasty operation in the Control group and 42 patients in the Intervention group. The Control group included 22 males and 23 females with a mean age of 65.36 ±6.9 years while Intervention group comprised 22 males and 20 females with a mean age of 65.14±4.06 years. Verbal rating pain scores, haemoglobin levels, haemorrhage amounts, blood transfusion amounts and hospital stay durations of the patients were detected. It was determined that all patients were applied elastic bandage for compression, 3 ml diclofenac sodium as the identical analgesic drug, 100 mg diclofenac tablets (Diclomec®, Abdi İbrahim, İstanbul, Turkey) twice daily and tramadol hydrochloride (contramal, Mefar İlaç, İstanbul, Turkey) once at the postoperative 6th hour. It was stated that Control group was administered standard cold application using ice packs with 15-minute periods for 8 times and intervals of 45 minutes on the operation day and postoperative 2nd day while operated knees of the Intervention group were applied c-pad (cryoceutical) preoperatively for 90 minutes until the operation and postoperatively for 6 hours on the operation day beginning just after the operation and for 2 hours in the following postoperative 2 days. The mean VRPS score of the Control group was 6.1 whereas VRPS score of the Intervention group was 6.6 (*P*>.05). The haemoglobin levels were assessed on the preoperative and postoperative 48th hours. The preoperative haemoglobin levels of the Control and Intervention groups were 13.12±1.3 g/dl and 12.5-9.1 g/d, respectively (*P*<.001). The postoperative haemoglobin levels of the Control and Intervention groups were 9.91±1.25 g/dl and 11.22±1.14 g/dl, respectively (*P*<.001). Postoperatively 24 hours later, the mean haemorrhage amounts of the Control and Intervention groups were 319.78±60.66 cc and 210.24±52.43 cc, respectively (*P*<.001). Need for blood transfusion (Hb≥8 g/dl) was present in 37 and 40 patients in the Control and Intervention groups, respectively. The mean hospital stay durations were 7.2±1.5 and 7.4±1.2 days, respectively (*P*=.756). It was reported that significant differences were discovered between the groups in terms of postoperative haemoglobin level and blood drainage amounts, however, no significant difference was present between two groups in terms of mean verbal rating pain scores, blood transfusion amounts and hospital stay durations. [16]

Bech et al. have carried out their study on totally 71 patients, 34 patients in the Control group and 37 patients in the Intervention group, between February 2009 and May 2012 and they evaluated the effects of cold ice pack and intermittent cooling device on the pain level, knee function score, rates of nausea and vomiting (between the postoperative 24th-48th hours), opioid use in terms of mg, change in haemoglobin levels in terms of g/l (between the postoperative 24th-48th hours), hospital stay duration and patient satisfaction rate in their study. The control group was applied cold ice pack intermittently for 48 hours during the general care of the patients and upon request whereas the Intervention group received cold application once for every 4 hours for postoperative 48 hours using intermittent cooling device. It was stated that both groups were administered fentanyl, oxycodone and morphine as analgesic drugs. The results of their study were detected as the following: Pain score (NRPS) Control group: 3.6; Intervention group: 3.8 (*P*=.67). Passive Range of Motion (PROM) test (postoperatively 48 hours later) Control group: 59.8; Intervention group: 54.0 (*P*=.14). Nausea and vomiting: Control group: 15.6%; Intervention group: 34.3%

(between the postoperative 24th-48th hours) (*P*=.08). Opioid use (between the postoperative 24th-48th hours), Control group: 42.3 mg; Intervention group: 49.9 mg (*P*=.33). The change in haemoglobin levels in terms of g/L (between the postoperative 24th-48th hours): Control group: -8.8; Intervention group: -7.7 (*P*=.68). The duration of hospital stay: Control group: 4.8 days, Intervention group: 5.8 days. Patient satisfaction: Control group: 63%, Intervention group: 96.9%. It was reported as the conclusion of this study that there was no significant difference between the Control group (applied cold ice pack intermittently for 48 hours) and the Intervention group (applied intermittent cooling device for 48 hours) in terms of pain score, passive ROM exercises, opioid use, haemoglobin levels, nausea-vomiting and duration of hospital stay whereas the Intervention group had significantly higher patient satisfaction. [17]

The study of Su et al. included totally 187 patients composed of Control group (n:84) patients who underwent total knee arthroplasty and were aging between 18-85 years and Intervention group (n:103) patients. It was found that assessments for pain level, Range of Motion (ROM) test, 6-minute walk test, assessments for the swelling rate around the knee and amount of analgesic drug use were performed in the postoperative 2nd-week and 6th-week evaluations. The same therapy protocol was implemented in the Control and Intervention groups. In addition, ice bag was applied in the Control group whereas the Intervention group received intermittent cooling air around the knee using cryopneumatic device. The postoperative 2nd-week evaluation revealed that the mean amount of morphine use was 680 mg ranging between 20-3225 mg in the Control group whereas the mean amount of morphine was 509 mg ranging between 15-1640 mg in the Intervention group (*P*< .05). Vas pain score (*P*=0) and swelling rate around the knee (*P*=0) were obtained. It was reported at the end of the postoperative 6th week that mean number of steps in the 6-minute walk test were 7.9 and 29.4 in the Control and Intervention groups, respectively (*P*=,13). It was denoted that there was no significant difference between the Control and Intervention groups in terms of VAS pain score during the postoperative 2nd week and besides two groups showed similar results in the 6-minute walk test, ROM test and assessment of swelling rate around the knee. It was reported that the Intervention group consumpted less amount of analgesic drug (morphine) and that there was a significant difference in favor of the Intervention group regarding only 6-minute walk test while no significant difference was encountered in terms of other parameters. [18]

In the study of Kullenberg et al. on 40 patients who underwent total knee arthroplasty in the Control group and 43 patients in the Intervention group; assessments of pain level (at the postoperative 1st and 3rd days, during the exercise), amount of analgesic drug use (drugs used at the postoperative 1st and 3rd days, during the exercise: tramadol, paracetamol), range of motion (ROM) test (at the postoperative 1st day, discharge and at the end of the 3rd week), decrease in the haemoglobin level and time to hospital discharge. The Intervention group was additionally administered cold compress once at 1 hour during 60 hours whereas control group received only routine therapy. The results of the study were presented as following: VAS pain score: Control group: 2.2 at the 1st day, 1.2 at the 3rd day, 2.3 during the exercise; Intervention group: 2.1 at the 1st day, 0.8 at the 3rd day, 3.4 during the exercise. Range of motion (ROM) test: Control group: 51.4° at the first day, 62.9° at discharge, 87.6° at the end of the 3rd week; Intervention group: 50.4° at the first day, 75.1° at discharge, 98.9° at the end of the 3rd week (*P*=.0045). Haemoglobin value: Control group: 109.5 mmol/L. Intervention group: 120.2 mmol/L (*P*=.042). The amount of analgesic use: Control group: 0.43 mg (mg morphine/kg per person) Intervention group: 0.37 mg (mg morphine/kg per person). Time to hospital discharge: Control group: 6.2; Intervention group: 4.8 (*P*=.002). This study demonstrated that cold compression therapy created a difference on pain level and amount of drug consumption, however this difference was not significant, whereas, cold compress therapy provided benefits on the parameters haemoglobin level and Range of Motion (ROM), thereby it can shorten the duration of hospital stay. [19]

Morsi. has evaluated totally 60 patients, 30 patients who underwent total knee arthroplasty in the Control group and 30 patients in the Intervention group. It was noted that continuous cooling air was postoperatively applied on the incision site in the Intervention group adjusted to keep the skin temperature at 7°C in the first 2 hours and subsequently 12°C whereas the Control group received routine treatment protocol. It was stated that assessments of pain level using Visual Analog Scales (VAS) (measured at the postoperative 1st and 2nd hours and once every 8 hours during the next 6 days), knee functions with range of motion (ROM) test (assessed during the first 6 weeks), haemorrhage amount (using hemovac drain during the first 48 hours), decrease in haemoglobin level, time to wound healing, amount of analgesic drug use (hydrocodone and acetaminophen for 6 days) were performed. Pain level: 6.3 in the Control group, 4.2 in the Intervention group (*P*< .001). Range of Motion (ROM) test: Control group: 54°. Intervention group: 68° at the first week (*P*< .01). There was

a difference between the 2nd-6th weeks, although not significantly. Haemorrhage amount (during 48 hours): Control group: 810 ml; Intervention group: 503 ml (*P*< .001). Mean haemoglobin loss: Control group: 4.6 mg; Intervention group: 2.9 mg (*P*<.001). No significant difference was found in terms of time to wound healing. The mean amounts of analgesic use in the groups were reported such as following: Control group: Administered 2.8 mg (1400 mg) drug, Intervention group: Administered 1.9 mg (950 mg) drug (*P*<.001). Compared with the Control group, it was stated that the Intervention group which received continuous cooling air therapy had lower pain level, higher range of motion, lower amount of haemorrhage and less reduction in haemoglobin level and significantly lower analgesic use whereas no significant difference in terms of time to wound healing. [20]

DISCUSSION

Serious complications such as pain condition, blood loss, changes in haemoglobin levels, oedema (swelling), restricted ROM, excessive analgesic consumption and consequent complications occur in the patients after total knee arthroplasty operation. The effect of cold application as a non-pharmacological treatment method as well as pharmacological therapy in the patients who experienced these complications was evaluated in the 7 literature studies enrolled in our review.

Pain is usually severe in the postoperative early period after total knee arthroplasty operation and it prevents rehabilitation. Mobilization requires pain control, however, side effects associated with narcotics (nausea, vomiting, sedation, itching, hypotension and respiratory distress) may limit the activity and they increase the morbidity, impair sleep quality, prolong hospital stay duration and reduces patient satisfaction. It is very important to achieve pain control while minimizing the side effects. [21-22] Thienpont et al., 2007. have reported in their study on 116 patients with TKP that cold application using cold packs is effective in reducing the postoperative swelling. [23] Levy and Marmar, 1993. have evaluated the effect of local cold application on improving in the patients who underwent total knee arthroplasty and reported that postoperative application of cold compress therapy decreased blood loss, swelling and pain and that increased range of motion in a shorter duration. [24] It has been encountered in the studies enrolled in the present systematic review that use of local cold application methods accompanied with pharmacological methods is an effective method in reducing pain and swelling and that it decreases analgesic consumption. Adie et al., 2012. have included that cold therapy showed a non-significant beneficial effect on blood loss, pain and ROM. [9] It has been noted also in the studies examined in our review that local cold application has a significantly positive effect on blood loss and ROM exercises. In addition, regarding haemoglobin levels, although there are some studies which denoted that no significant difference was found between the groups, the literature studies included in our review have reported significant differences between the groups.

In NRS-2002 screening test, nutritional risk is considered for scores ≥3. [10] In a previous study, the malnutrition risk among hospitalized oncology patients was reported as 33.9% upon admission. [11] However, only 1.9% of our patients were ≥3 score in NRS-2002 at our service. Compared with the literature, the malnutrition risk rate was low in our inpatient clinic. Also, the percentage of overweight patients was higher than our underweight patients. One of the reasons for the low malnutrition rate may be the nature of cross-sectional retrospective study in which we do not know previous treatment of malnutrition or any other interventions. Also, the majority of our patient population is younger than 65 years old, which might have an effect on the low NRS-2002 score. Another possible reason for the low malnutrition rate in our series could be hospitalization due to transportation problems to the RT unit.

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To our knowledge, synergistic effect between RT and chemotherapy increased acute hospital admissions from 20% in RT only group to approximately 60% in concurrently treated group. [9] This might have an effect on nutritional status of our hospitalized patients. However, we are unable to provide our patients' concurrent chemotherapy information.

Table 1. Overview of the literature

Author and publishment year	Research Title	Sampling Features	Pain	Swelling	Knee Society Function Score (KSS)	Haemorrhage amount	Haemoglobin values	Analgesic-Opioid use
Li et al.[14]	Effects of Cold Irrigation on Early Results after Total Knee Arthroplasty	Randomized, Double-blind, Controlled Study Control (n:192) Intervention (n:197)	VAS pain score within the first 4 hours ***P*=.00.** At the end of 24 hours ***P*=.00.**	Swelling at the operation site at the end of 48th hour Control: 2.3 cm. Therapy: 1.9 cm ***P* = .0007**		Postoperative 24 hours later Control: 155.8 ml Intervention: 130.6 ml ***P* <.001**	Control: 30.2 g/dl Intervention: 26.1 g/dl ***P* <.001**	Analgesic use: 0-12 hours ***P* = .0033**. 12-24 hours ***P* = .0021**.
Kuyucu et al.[15]	Is cold therapy really effective after knee arthroplasty?	Randomized Controlled Study Control group (n:33) Intervention group (n:27)	VAS Pain Score Control: 3.3-4.5 Intervention: 2.1-3.0 ***P* < .05**		Control: 80.3% Intervention: 90.5% ***P* <.05**	Control: 12.8-9.0 mmol/dl Intervention: 12.5-9.1 mmol/dl (***P* >.05** for all days)	Postoperative haemorrhage Control: 400.4 (140-650) cc Intervention: 365 (150-900) cc (***P* >.05** for all days)	
Desteli et al. [16]	Effect of both preoperative and postoperative cryoceutical treatment on haemostasis and postoperative pain following total knee arthroplasty	Randomized Controlled Study Control group (n:45) Intervention group (n:42)	VRPS Pain Score Control: 6.1 Intervention: 6.6. ***P* <.05**			Haemorrhage amount postoperative 24 hours later Control: 319.78± 60.66 cc Intervention: 210.24±52.43 cc ***P* <.001**	Postoperative haemoglobin Control: 9.91±1.25 g/dl Intervention: 11.22-1.14 g/dl. ***P* < .001**	
Bech et al. [17]	Device or Ice: The Effect of Consistent Cooling Using a Device Compared with Intermittent Cooling Using an Ice Bag after Total Knee Arthroplasty	Randomized Controlled Study Control group (n:34) Intervention Group (n:37)	NRP Pain score Control: 3.6 Intervention: 3.8 ***P* =.67.**		PROM test (48 hours after surgery) Control: 59.8 Intervention: 54.0 ***P* =.14**		Postoperative 24-48 hours Control: -8.8 Intervention: -7.7 ***P* =.68**	

Su et al. [18]	A prospective, multicentre, Randomized trial to evaluate the efficacy of a cryopneumatic device on total knee arthroplasty recovery	Prospective, multicentre, Randomized Controlled Study Control group (n: 84) Intervention group (n:103)	VAS pain score ***P* = 0**	Swelling rate around the knee: ***P* = 0**				Morphine use in control group: Ranging Between 20-3225 mg Mean: 680 mg morphine use in the intervention group: Ranging between 15-1640 mg. Mean: 509. ***P* <.05**
Kullenberg et al. [19]	Postoperative Cryotherapy After Total Knee Arthroplasty	Prospective, Randomized Controlled Study (n:83) Control group: (n:40) Intervention Group: (n:43)	VAS pain score Control group: 3.4 Intervention group: 2.3 ***P* <.05**		ROM: Control: 1st day: 51.4° At discharge: 62.9°. At the end of 3rd week: 87.6° Intervention group: 1st day: 504°. At discharge: 75.1°. At the end of 3rd week: 98.9° ***P* = .0045**		Control: 109.5 mmol/L Intervention: 120.2 mmol/L ***P* =.042**	Analgesic use Control group: 0.43 (mg morphine/kg per person) Intervention group: 0.37 (mg morphine/kg). ***P* < .001**
Morsi [20]	Continuous-flow cold therapy after total knee arthroplasty	Prospective, Randomized Controlled Study Control (n: 30) Intervention: (n:30)	VAS pain score Control group: 6.3 Intervention group: 4.2 ***P* < .001.**		Mean Range of Motion (ROM) at 1st week: Control group: 54° Intervention group: 68° ***P* <.01**	Mean haemorrhage amount (for 48 hours) Control: 810 ml. Intervention: 503 ml ***P* < .001.**	Mean haemoglobin loss Control: 4.6 mg Intervention: 2.9mg ***P* < .001**	Analgesic use: Control group: Used 2.8 (1400 mg) tablets, Intervention group: Used 1.9 (950 mg) tablets ***P* < .001**

This study has limitations inherent to any retrospective study as missing information about follow up. In previous studies, both BMI and weight loss independently predicted the overall survival of cancer patient. [4] However, we were unable to report that follow up information of our patients' weight loss, nutritional intervention, second NRS-2002 score results. Also, we do not have specified data about nutritional interventions, chronic diseases and concurrent chemotherapy. These might have an effect on low malnutrition screening ratio of our inpatients.

As a summary, we aimed to look at nutritional status of patients in radiation oncology inpatient unit from a cross sectional view in this study. When we screened the risk of malnutrition of inpatients in the radiotherapy inpatient service using the NRS 2002 test, we did not detect an increased risk in our study. Further research is required in order to optimize nutritional intervention and follow up data for evaluating the nutritional status of patients in radiation oncology inpatient service.

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Giant Solitary Fibrous Tumour of The Orbit Resected via Subconjunctival Approach

Orbital Dev Soliter Fibroz Tümörün Subkonjunktival Yaklaşımla Rezeksiyonu

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ABSTRACT

Solitary fibrous tumours (SFTs) are uncommon neoplasms originating primarily in the pleura but occasionally in the orbit. Despite their generally benign nature, they can exhibit aggressive behaviour. This study focuses on a rare case of a giant SFT located in the orbit, emphasizing diagnostic challenges and treatment considerations. A 69-year-old male with a history of progressive eyelid swelling, proptosis, and vision loss underwent a subconjunctival approach for the removal of an orbital SFT. Histopathological analysis, along with immunohistochemistry markers, confirmed the tumour's identity. Successful tumour resection was achieved through the subconjunctival approach, highlighting the efficacy of this method for orbital SFTs. The histopathological examination revealed typical features of SFT, characterized by spindle cells and unique architectural patterns. Immunohistochemistry further supported the diagnosis. This case underscores the importance of considering orbital SFTs in the differential diagnosis of orbital tumours, particularly when confronted with proptosis and visual disturbances. Surgical excision, guided by radiological imaging and immunohistochemically analysis, remains the primary therapeutic approach. However, due to the potential for aggressive behaviour, further research is needed to optimize management strategies, especially in cases of incomplete resection or atypical behaviour.

Keywords: Solitary fibrous tumour, orbit, subconjunctival approach, proptosis, differential diagnosis

ÖZ

Yalnız fibrous tümörler (YFT), genellikle plevradan kaynaklanan nadir neoplazmlardır, ancak nadir durumlarda orbitada da görülebilirler. Genel olarak benign nitelik taşımasına rağmen agresif davranışlar sergileyebilirler. Bu çalışma, orbitada yer alan nadir bir dev YFT vakasına odaklanarak tanısal zorlukları ve tedavi düşüncelerini vurgulamaktadır. İlerleyici göz kapağı şişliği, proptozis ve görme kaybı öyküsüne sahip 69 yaşındaki erkek hasta, orbitadaki bir YFT'nin çıkarılması için subkonjonktival yaklaşım uygulandı. Histopatolojik analiz ile immünohistokimya işaretleri, tümörün kimliğini doğruladı. Başarılı tümör çıkarılması, subkonjonktival yaklaşımın orbitadaki YFT'ler için etkililiğini göstermektedir. Histopatolojik inceleme, iğsi hücreler ve benzersiz mimari desenlerle karakterize edilen tipik YFT özelliklerini ortaya çıkardı. İmmünohistokimya, tanıyı daha da destekledi.Bu vaka, özellikle proptozis ve görme bozuklukları ile karşılaşıldığında orbital tümörlerin ayırıcı tanısında orbital YFT'leri düşünmenin önemini vurgular. Radyolojik görüntüleme ve immünohistokimyasal analiz rehberliğinde cerrahi çıkarılma, temel tedavi yaklaşımını oluşturur. Bununla birlikte, agresif davranış potansiyeli nedeniyle, eksik çıkarılma veya atipik davranış durumlarında yönetim stratejilerini optimize etmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Soliter fibrous tümör, orbita, subkonjonktival yaklaşım, proptozis, ayırıcı tanı

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INTRODUCTION

Solitary fibrous tumours (SFTs) are rare neoplasms that primarily originate in the pleura but can also occur in the orbit, although their occurrence in this location is uncommon. [1] Typically, patients affected by orbital SFTs present with progressive swelling of the eyelids, proptosis, and visual disturbances [2]. Unlike SFTs occurring in pleural sites, orbital SFTs do not exhibit systemic symptoms such as hypoglycaemia, arthralgia, or pleural or peritoneal effusion. [2] However, it is important to consider the possibility of the meningeal variation of solitary fibrous tumours with orbital involvement in the differential diagnosis of aggressive dural-based lesions. [3]

Although solitary fibrous tumours are generally considered benign neoplasms, they can exhibit aggressive behaviour, including high rates of local recurrence and the potential for late-term metastasis to the bones and lungs. [4] These tumours have been known to extend from the orbit to adjacent structures such as the paranasal sinuses, extradural anterior and middle cranial fossas, cavernous sinus, and other cranial regions through the orbital fissures or foramina. Despite their rarity, it is crucial to recognize the clinical features and potentially aggressive nature of orbital solitary fibrous tumors. Complete surgical excision of the tumour is the primary treatment approach, which can significantly reduce the associated clinical symptoms. However, in cases where orbital involvement of meningeal solitary fibrous tumours is suspected, a careful differential diagnosis is essential due to their potential aggressiveness. [3]

CASE PRESENTATION

A 69-year-old male patient presented with a six-year history of swelling in the right upper and lower eyelids, accompanied by eye extrusion and vision loss. The patient had previously undergone two surgeries due to a right frontonasal tumour that extended into the orbit. **(Figure 1 A and B)** Total vision loss was noted in the right eye. External examination revealed increased periorbital pigmentation and 7 mm of exterior displacement of the right globe. Surgical excision scars from the previous transcranial procedures were observed in the right frontozygomaticoorbital region. A computed tomography (CT) scan demonstrated a solid extra-conal mass measuring 4×3×4 cm, adhering to the lateral-superior wall of the right orbit and the orbital roof. The tumour extended into the left lateral subfrontal space. Based on a provisional diagnosis of a soft tissue tumour, the patient underwent a right subconjunctival approach for tumour resection. **(Figure 1 C and D, Figure 2)**

Under general anaesthesia, the patient was fully prepped and draped, and traction sutures were placed in the center of the tarsal plates of both upper and lower lids. A lid speculum was used to keep the globe exposed and the eyelids opened. A superolateral conjunctival peritomy was performed around the frontozygomatic hemi-limbus, and Tenon's capsule was dissected free from the globe until the tumour mass was reached in the superolateral region. Careful blunt dissection was then performed around the tumour, utilizing the best available tumour tissue plane. The tumour's capsule, which adhered to neighbouring tissues, was reached and a grayish, soft tumour mass was resected and cauterized using bipolar cautery. The tumour was then freed from the lateral orbit and completely resected. A gross examination of the tumour revealed a well-circumscribed and pseudo-encapsulated mass with dimensions ranging from 3x4x4 cm. Upon cut section, the tumour displayed a grayish and fleshy appearance with areas of haemorrhagic foci. Macroscopically, the tumour had a soft-elastic consistency and a grayish surface. The patient was followed up for six months, and a second operation was planned to achieve total resection of the tumour using a sub-conjunctival approach.

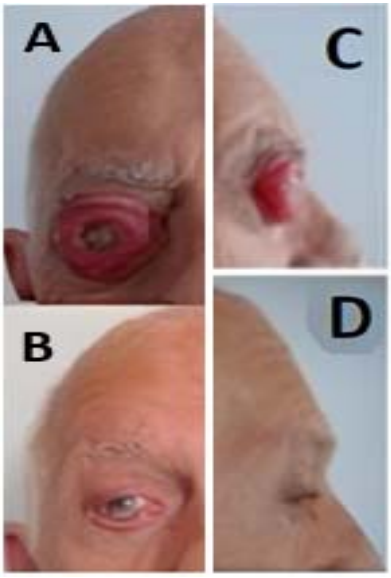

Figure 1: External photograph showing a superior-temporal displacement of the globe with a firm lobulated mass felt along the inferonasal orbit and conjunctiva, with scarring of the cornea.

Histopathological examination of the resected tumour revealed a dense proliferation of spindle cells with variable architectural patterns. There were areas with a fascicled pattern as well as areas with a random and "pattern-less" cell arrangement. The spindle cells showed uniform, oval-shaped nuclei with finely dispersed chromatin.

Immunohistochemistry analysis demonstrated strong and diffuse positivity for CD34, CD99, and bcl-2 in the tumour cells, while S-100 protein and CD45 were negative. **(Figure 3, 4)**

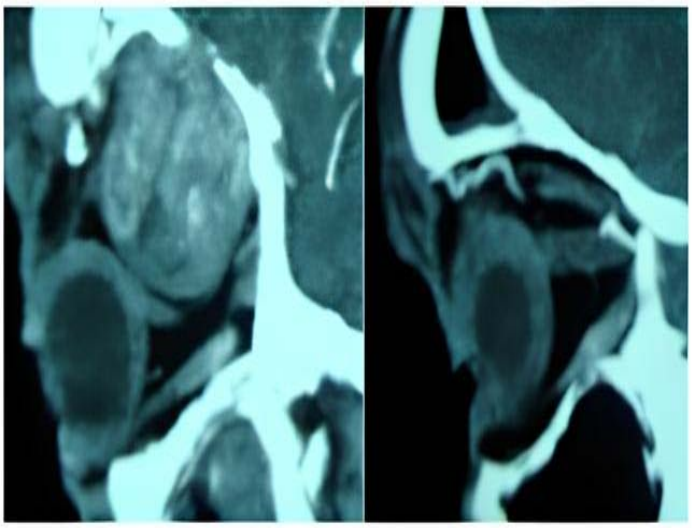

Figure 2: Computerized tomography of the orbit revealed an intensely enhancing well-circumscribed large orbital mass lesion measuring 5 × 4.8 × 4.5 cm and post-operative image.

DISCUSSION

Solitary fibrous tumours (SFTs) primarily originate from the pleura but can also occur in the orbit as rare spindle cell neoplasms. While their occurrence in the pleural region has been extensively studied, orbital SFTs are relatively uncommon, and there have been limited case reports and series documenting their characteristics. [1] Orbital SFTs present progressive swelling of the upper eyelid and proptosis, with accompanying visual disturbances. Although generally benign in nature, SFTs can exhibit aggressive behaviour, necessitating thorough evaluation and appropriate differential diagnosis for aggressive dural-based lesions. [3]

The differential diagnosis of orbital SFTs includes hemangiopericytoma, among other conditions. This section elaborates on the distinguishing features of these conditions, guiding clinicians in accurate diagnosis. The similarities and differences between these entities are crucial for proper therapeutic planning.

The age range of patients with orbital SFTs typically spans from 33 to 75 years. Surgical resection is the primary treatment modality, with various approaches employed depending on the tumour location. Complete excision of the tumour is associated with favorable outcomes, while incomplete resection is a significant risk factor for tumour recurrence. The role of postoperative radiotherapy in managing atypical or incompletely resected central nervous system SFTs is still under investigation and requires further study. [5]

Radiological imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), play a crucial role in diagnosing and evaluating orbital SFTs. These tumours often display marked enhancement on postcontrast CT and MR images. Dual-phase CT scans may reveal rapid enhancement followed by early washout of contrast material. Furthermore, cerebral angiography can provide insight into the rich vascular supply feeding the tumour through branches of both the external and internal carotid arteries. [6]

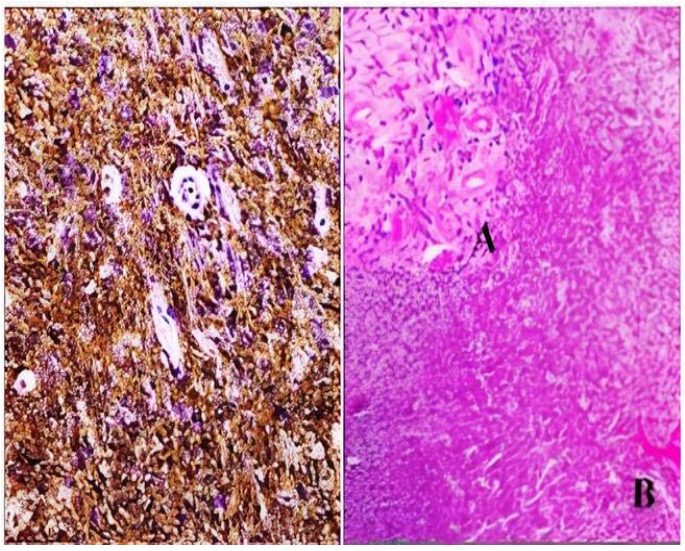

Figure 3: Microscopic aspect of a solitary fibrous tumor: Plump spindle cells with round or oval vesicular nuclei and prominent vascularity.

Histologically, orbital SFTs exhibit high cellularity and significant pleomorphism. Immunohistochemically analysis is essential for confirming the diagnosis and differentiating SFTs from other neoplasms. CD34 and vimentin are commonly employed markers, displaying diffuse positive staining in SFTs. Conversely, SFTs typically exhibit negative staining for cytokeratin, epithelial membrane antigen, glial fibrillary acidic protein, S-100 protein, and factor XIII. [7] While histologic appearance can vary, complete resectability remains the most critical prognostic factor for both orbital and pleural SFTs. [9]

Clinical awareness of orbital SFTs as a potential cause of unilateral proptosis is essential. These tumours can present with both benign and malignant behaviour. Malignant forms

may invade local structures, demonstrate recurrent growth, or metastasize, while benign lesions can often be effectively cured through surgical excision. Therefore, including orbital SFTs in the differential diagnosis of unilateral proptosis is paramount, along with the utilization of immunohistochemically markers to ensure accurate diagnosis. [8]

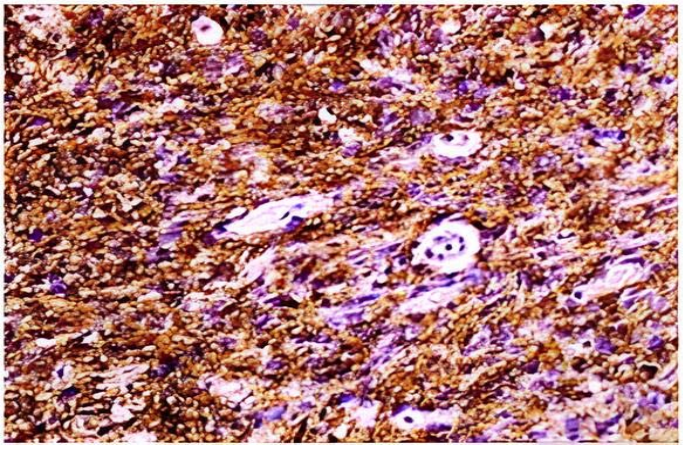

Figure 4: Immunohistochemically exam, showing strong positivity of tumour cells to CD34.

This case underscores the importance of considering a broad age range for patients with orbital SFTs. While the typical age range is 33-75 years, cases outside this spectrum are not uncommon. The role of advanced imaging techniques like MRI and comprehensive immunohistochemically analysis is crucial in the diagnosis and treatment planning of orbital SFTs. The study also discusses the potential for aggressive behaviour and recurrence, emphasizing the need for thorough surgical resection and close follow-up.

Orbital SFTs, while rare, should be considered in the differential diagnosis of orbital tumours across a wide age range. This case highlights the importance of modern imaging techniques and extensive immunohistochemically profiling in the management of these tumours. Further research is encouraged to deepen understanding and improve treatment strategies, particularly in cases of incomplete resection or atypical behaviour.

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Düşük Doz Steroid Tedavisi Sonrası Gelişen CMV Reaktivasyonu

CMV Reactivation after Low Dose Steroid Treatment

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ÖZ

Cytomegalovirus (CMV) insandan insana bulaşan ve ömür boyu latent kalabilen bir virüstür. Primer enfeksiyonu daha sıklıkla gribal şikâyetlerle çocukluk döneminde karşımıza çıkmaktayken vücutta latent kalarak özellikle immunsupresan durumlarda reaktivasyon enfeksiyonları yetişkinlik çağında görülebilmektedir. CMV sendromu ya da pnömoni, hepatit, retinit, kolit gibi end-organ CMV hastalığı olarak klinik vermektedir. Kortikosteroid kullanımı CMV reaktivasyonu için risk faktörüdür. Astım harici bilinen kronik hastalığı olmayan 27 yaşındaki kadın hasta ateş, halsizlik, nefes darlığı şikâyetleri ile dış merkezde tetkik edilmiş, verilen antibiyoterapilere rağmen klinik yanıt alınamaması ve tanı konulamaması üzerine hastanemize başvurdu. Nedeni bilinmeyen ateş ön tanısıyla yatırıldı ve ateş etyolojisinde rol oynayan tanılar dışlandı. CMV Ig M ve G pozitif, avidite düşük olarak sonuçlandı. Hastanın 3 yıl önce yapılan tahlillerinde CMV IgG pozitifliği olduğu görüldü. Alınan CMV PCR sonucu 46960 copy/mL olarak sonuçlandı. Hastanın anamnezinde astım atağı sebebiyle acil başvurularında intravenöz olarak ve ardından oral olarak kortikosteroid alma öyküsü olması sebebiyle CMV reaktivasyonu tanısı konuldu. Gansiklovir tedavisinin ardından ateşi düşen ve kliniği düzelen hasta CMV PCR sonucunun negatifleşmesi görüldükten sonra şifa ile taburcu edildi. CMV reaktivasyonu düşük doz kısa süreli steroid tedavileri sonrası da gelişebilmekte olup hastalara steroid verilirken dikkatli olunmalıdır. Nedeni bilinmeyen ateş etyolojisinde CMV'nin de olduğu akılda tutulmalıdır.

Anahtar Kelimeler: Sitomegalovirus, reaktivasyon, kortikosteroid, enfeksiyon hastalıkları.

ABSTRACT

Cytomegalovirus (CMV) is a virus transmitted from person to person, capable of remaining latent throughout a person's life. While primary infection often manifests with flu-like symptoms in childhood, reactivation infections can occur in adulthood, especially in immunosuppressed conditions. CMV presents clinically as syndromes or end-organ diseases such as pneumonia, hepatitis, retinitis, and colitis. The use of corticosteroids is identified as a risk factor for CMV reactivation. A 27-year-old female patient with no known chronic diseases, except asthma, initially sought care at another facility. there, a diagnosis could not be established and the administered antibiotic were ineffective. Subsequently, she was referred to our hospital. In our hospital initially other potential diagnoses causing fever were ruled out. CMV IgM and IgG were positive; Ig G was with low avidity. In the patient's previous tests, CMV IgG positivity from 3 years ago was identified. CMV PCR results indicated 46960 copies/mL. The patient's history of receiving intravenous and oral corticosteroids for asthma exacerbation led to the diagnosis of CMV reactivation. Following ganciclovir treatment, the patient's fever subsided, and upon negative CMV PCR results, she was discharged in good health. CMV reactivation can occur after low-dose short-term steroid treatments. CMV should be considered in the etiology of unexplained fever.

Keywords: Cytomegalovirus, reactivation, corticosteroid, infectious diseases

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GİRİŞ

Cytomegalovirus (CMV), Herpesviridae ailesine ait bir DNA virüsüdür. Virüsün adı, enfekte hücrede büyümeye neden olarak mikroskop altında görülen karakteristik inklüzyon cisimlerinden türetilmiştir . Bulaşı; tükürük, idrar, gözyaşı, kan veya genital salgılar gibi vücut sıvıları aracılığıyla gerçekleşir. [1] CMV, ilk enfeksiyonun ardından bağışıklık sisteminden temizlenmeyi başarıyla engeller ve nötrofillerde, T lenfositlerde, endotel hücrelerinde ömür boyu varlığını sürdürerek insan nüfusunun büyük bir kısmında kalıcı bir enfeksiyona neden olur. [2] Dünya genelinde CMV'nin seropozitiflik oranı %45 ile %100 arasında değişmektedir. [1] CMV enfeksiyonu, immün sistemi normal olan bireylerde yaygın bir durum değildir ancak bağışıklık sistemi baskılanmış bireylerde reaktive olarak doku tutulumları yapabilir. [3] Primer veya reaktive CMV enfeksiyonları genellikle edinilmiş bağışıklık yetmezlik sendromu (AIDS) hastalarında, organ nakil hastalarında, malignite hastalarında, steroid veya immünsüpresan alan hastalarda fırsatçı enfeksiyonlar olarak gözlenir. [4] Klinik belirtiler, hafif grip benzeri ateşli hastalıktan (özellikle primer enfeksiyonda) yaşamı tehdit eden doku-invaziv end-organ hastalığına kadar geniş bir yelpazede değişir. CMV; retina, solunum sistemi, merkezi sinir sistemi, gastrointestinal sistemi, hematolojik sistemi etkileyebilir; özofajit, kolit, pnömoni, hepatit, ensefalit, retinit, miyokardit, hemolitik anemi, portal ven trombozu yapabilir. [5]

CMV hastalığının tanısı anamnez, fizik muayene, laboratuvar testleri ve klinik bulgulara dayanır. Genellikle ateş, halsizlik, atipik lenfositoz, lökopeni veya nötropeni, trombositopeni ve yüksek karaciğer transaminazları olarak kendini gösteren CMV sendromu ve end-organ CMV hastalığı (pnömoni, hepatit, retinit vb.) olmak üzere iki kategoriye ayrılır. Uygun klinik semptomların veya belirtilerin yanında ilgili organ dokusunda CMV'nin histopatolojik olarak gösterilmesi, dokuda virüs izolasyonu ve bazı durumlarda kanda CMV DNA miktarının gösterilmesiyle; primer enfeksiyonda ise serokonversiyonun gösterilmesiyle tanı konur. [6] CMV enfeksiyonunu tedavi etmek için şu anda yaygın olarak tercih edilen ilaç, intravenöz gansiklovir tedavisidir. Gansiklovirin bir türevi olan valgansiklovir, oral biyoyararlanımı olan bir gansiklovir proilacıdır ve rutin olarak solid organ nakli alıcılarına CMV profilaksisi olarak verilir. Valgansiklovir, özellikle GCV'ye dirençli durumlarda etkili bir seçenek olabilir. [7]

OLGU SUNUMU

27 yaşında kadın hasta 3 hafta önce nefes darlığı şikâyetiyle birkaç defa acil servise başvurmus, astım atağı sebebiyle intravenöz yoldan ve nebulizatörlerle tedavi verilmiş. Astım haricinde kronik hastalığı yokmuş. Göğüs hastalıkları tarafından mevcut bronkodilatörlerine ek günlük 64 mg metilprednizolon tablet reçete edilmiş ve hasta 6 gün kullanmış. Bu durumdan yaklaşık 5 gün sonra başlayan üşüme, titreme, ateş, nefes darlığı şikâyetleriyle dış merkeze başvurmuş ve yatırılarak 8 gün tetkik ve tedavi edilmiş. Şikâyetlerinin geçmemesi üzerine kendi isteğiyle hastanemize başvurmuş. Hastanın epikrizinde enfeksiyon odağı araştırıldığı ancak bulunamadığı; 3 gün seftriakson, 2 gün piperasilin tazobaktam, 3 gün meropenem tedavisi verildiği fakat ateş yanıtı alınamadığı yazılmıştı.

Hasta nedeni bilinmeyen ateş ön tanısı ile kliniğimize yatırıldı. Genel durumu orta, bilinç açık, oryante ve koopere idi, halsiz görünümü mevcuttu. Fizik muayenesinde batında defans rebound yoktu, hepatosplenomegali saptandı. Solunum sesleri bibaziller azalmıştı ve apikallerde ronküs mevcuttu. Bu bulgular dışında diğer sistemlerin fizik muayenesinde ek özellik yoktu. Oksijen saturasyonu oda havasında %80'di, diğer vitalleri stabildi. Yatışı boyunca 38-39°C dereceyi geçen ateşi ve eşlik eden taşikardisi, takipnesi ve saturasyon düşüklüğü oldu. Hastanın kan ve balgam kültürleri, serolojik testleri, hemogram biyokimya tetkikleri istendi. Yapılan laboratuvar tetkiklerinde beyaz küre sayısı (WBC) 16090 /µL (nötrofil %44,3, lenfosit %45,6, monosit %8,3), trombosit sayısı 160000 /µL, hemoglobin

11,1 g/dL, Aspartat aminotransferaz (AST) 28,3 U/L, Alanin aminotransferaz (ALT) 54,6 U/L,

Laktat dehidrogenaz (LDH) 433,5 U/L, total protein 5,2 g/dL, albumin 2,4 g/dL, INR 1,1 sn, C-Reaktif Protein (CRP) 20 mg/L olarak saptandı. Ampirik olarak moksifloksasin günde bir kez 400 mg intravenöz tedavisi başlandı. Brucella, EBV, toksoplazma, HIV, sifiliz, quantiferon tetkikleri negatifti. Solunum yolu patojen etkenleri hızlı PCR tetkikinde pozitif sonuçlanan olmadı. Yapılan ekokardiyografide enfektif endokardit lehine bulgu saptanmadı. Göğüs hastalıkları akciğerde pnömonik odak olmadığını doğruladı. PPD sonucu 2 mm ölçüldü. CMV Ig M ve G pozitif, avidite düşük olarak sonuçlandı. Batın, lenf bezi ve jinekolojik ultrasonda splenomegali dışında ek patoloji saptanmadı. Dahiliye lenfomonositoz açısından periferik yayma ile hematolojik maligniteler açısından değerlendirdi, periferik yaymada blast izlenmediğini, dev trombositler dışında patoloji görülmediğini belirtti. Romatolojik hadiseler açısından alınan otoimmun markerları negatif sonuçlandı. Bu süreçte, yatışının 4. gününde olan hastanın ateşi günde 2 ya da 3 kez 38°C derecenin üzerine çıkmaktaydı. Hemogram takiplerinde WBC sayısı 310090 /µL'ye, CRP ise 75 mg/L kadar yükseldi. Hiçbir kan kültüründe ve balgam kültüründe

üreme olmadı.

CMV tetkikleri tekrarlandığında aynı şekilde CMV Ig M ve G pozitif, avidite düşük olarak sonuçlandı. Hastanın 3 yıl önce yapılan tahlillerinde CMV IgG pozitifliği olduğu görüldü.

Alınan ilk CMV PCR sonucu 8730 copy/mL iken 4 gün sonra alınan CMV PCR sonucu 46960 copy/mL olarak sonuçlandı. Başka hiçbir klinik neden veya laboratuvar sonucu, mevcut ateşli hastalığı açıklamadığı için hastanın düşük doz steroid tedavisi sonucu CMV reaktivasyonu geliştirdiği sonucuna varıldı.

Hastaya gansiklovir 5 mg/kg, 12 saat arayla intravenöz şekilde tedavisi başlandı ve moksifloksasin tedavisi kesildi. Ateşi tedavinin ikinci gününden sonra tekrarlamadı. Hastanın genel durumu 1 hafta içinde düzeldi. Gansiklovir tedavisinin 7. gününde alınan PCR 1280 copy/mL olarak sonuçlanırken 14. ve 20. gününde alınanlar negatif sonuçlandı. 21 günlük gansiklovir tedavisinin ardından hasta şifa ile taburcu edildi.

TARTIŞMA

CMV reaktivasyonuyla sıklıkla ilişkilendirilmiş olan durumlar solid organ veya kemik iliği malignitesi, nötropeni, sistemik glukokortikoidlerin kullanılması, teşhis edilmiş bağışıklık yetersizliği (kemik iliği ya da solid organ transplantasyonu, HIV pozitifliği)dir. [8] Glukokortikoidlerin varlığında CMV'nin litik replikasyonunun arttığı invitro olarak gösterilmiştir. [9] Organ nakil hastalarında reddi önlemek için kortikosteroidli kombinasyonlar verildiğinde CMV reaktivasyonunun arttığı bilinmektedir. [10] İnflamatuar bağırsak hastalığı tedavisinde steroid kullanımının yaygın olduğu yıllar ile steroid bazlı rejimlerin terk edildiği yılların CMV reaktivasyon oranı kıyaslandığında CMV kolitinin steroid bazlı rejimlerde çok daha yüksek olduğu görülmüştür. [11] 52 hastadan oluşan bir çalışmada dermatomiyozit tanısı sebebiyle devamlı steroid kullanan hastalarda CMV geliştikten sonra analiz yapılmış, steroid kullanımından CMV reaktivasyonunun saptanmasına kadar geçen ortalama süre 6 hafta, CMV reaktivasyonu tanısına kadar geçen toplam oral prednizolon miktarı 2000 mg olarak saptanmış. [12] Akciğer nakli hastaları içinde CMV reaktivasyonu geçiren 39 hasta üzerinde yapılan araştırmada median olarak 273 günde reaktivasyon geliştiği, 0.5-0.75 mg/kg/gün prednisolon tedavisi almanın anlamlı risk faktörü olduğu bulunmuştur. [13] Hematopoetik nakil alıcıları içinde 55 CMV reaktivasyonu olgusunda yapılan başka bir çalışmada haftalık 600 mg prednizolonun üzerinde steroid kullanan kişilerde, daha az steroid kullananlara göre anlamlı seviyede fazla CMV geliştiği saptanmış. [14] Ayrıca ek immunsupresif patoloji olmaksızın, kısa süreli ya da düşük doz steroid alımı sonrası CMV reaktivasyon vakaları da bildirilmiştir. [15]

SONUÇ

İmmunsupresif tedavi kullanımları ya da immun yetmezliğe sebep olan hastalıkların sayısı dünya genelinde artmaktadır ve bu durum CMV reaktivasyonu sayısını da artırmaktadır. Vakamızda olduğu gibi glukokortikoidlerin kısa süre düşük dozlarda alınması dahi CMV reaktivasyonu için risk oluşturmaktadır ve ayırıcı tanılarda akılda tutulması gerekmektedir. Nedeni bilinmeyen ateş olgularında viral etyolojilerin de olabildiği unutulmamalıdır.

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