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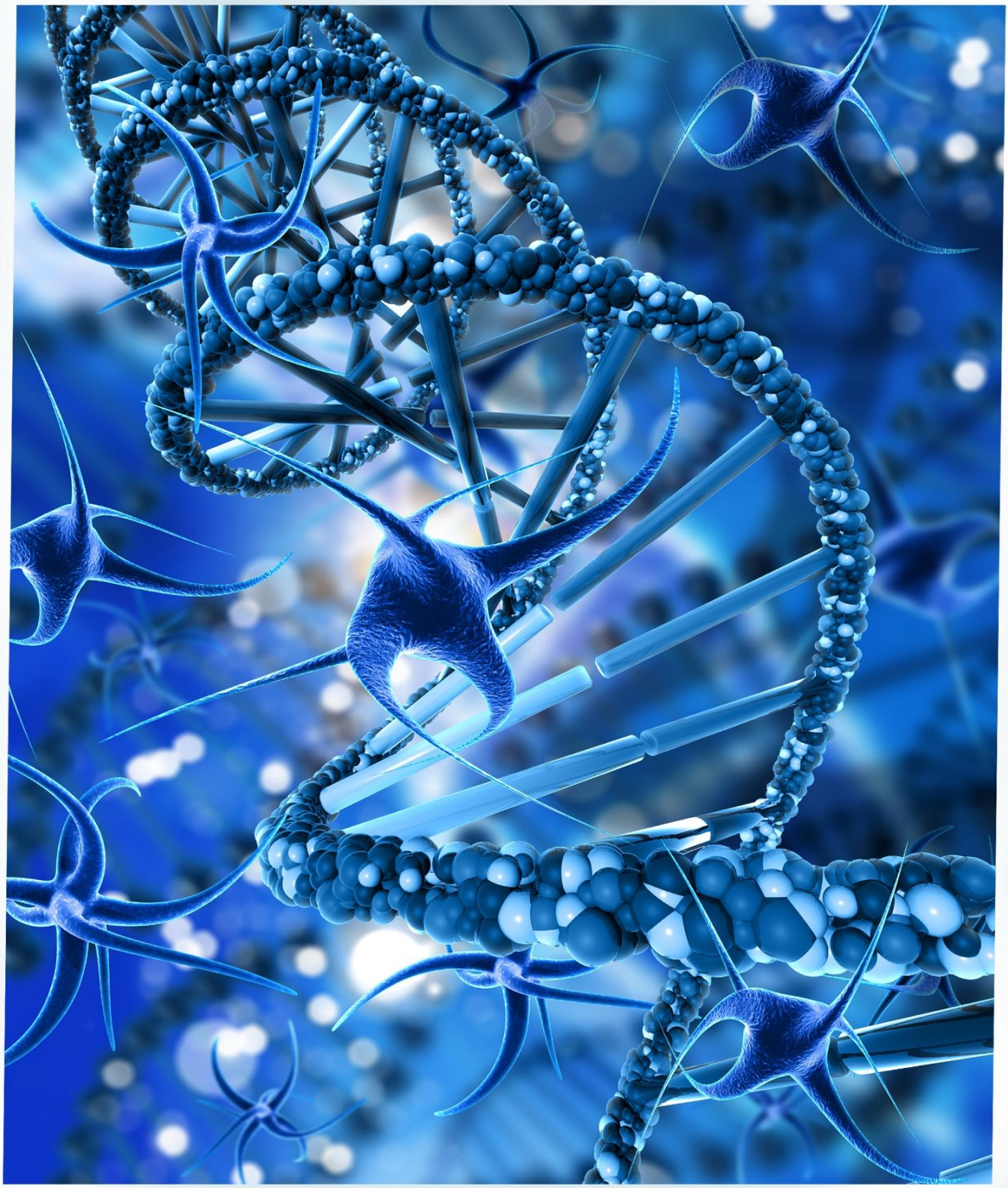

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Evaluation of Therapeutic Effect of Chrysin against 5-Fluorouracil-Induced Ovarian Damage in Rats

Sıçanlarda 5-Florourasil Kaynaklı Yumurtalık Hasarına Karşı Krisinin Terapötik Etkisinin Değerlendirilmesi

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ABSTRACT

5-fluorouracil (5-FU) is an effective and widely used chemotherapeutic agent to treat various malignancies, but its therapeutic use is limited due to dose-related tissue toxicity. Many studies have confirmed that oxidative stress and inflammation play a major role in the pathogenesis of 5-FU-induced damage in the various tissues. Chrysin (CHS), a natural flavone, exhibits various beneficial activities, including antioxidant, anti-inflammatory and anticancer. The aim of this study was to determine the therapeutic effect of CHS against 5-FU-induced oxidative stress and inflammation in the ovary tissue of rats for the first time. Thirty female rats were divided into 5 groups: control, 5-FU (100 mg/kg), 5-FU+CHS (1 mg/kg), 5-FU+CHS (2 mg/kg) and CHS (2 mg/kg). 5-FU treatment was administered intraperitoneally (i.p.) on the first day and CHS (i.p.) were applied for the following 3 days. The ovarian tissue levels of malondialdehyde (MDA), total oxidant status (TOS), total antioxidant status (TAS), 8-hydroxy-2'-deoxyguanosine (8-OHdG), catalase (CAT) and interleukin-6 (IL-6) were determined using spectrophotometric methods. MDA, TOS, 8-OHdG and IL-6 levels were significantly higher ($p<0.05$) and TAS and CAT levels level were significantly lower ($p<0.05$) in the 5-FU group than in the control group. CHS treatments significantly restored the levels of oxidative stress and inflammation parameters in a dose-dependent manner ($p<0.05$). Our results suggest that CHS can have a therapeutic effect against 5-FU-induced ovarian damage and therefore the use of CHS after chemotherapy may be beneficial in abolishing 5-FU-induced reproductive toxicity.

Keywords: 5-fluorouracil, Chrysin, Inflammation, Ovarian damage, Oxidative stress, Rat

ÖZET

5-florourasil (5-FU), çeşitli maligniteleri tedavi etmek için etkili ve yaygın olarak kullanılan bir kemoterapötik ajandır, ancak doza bağlı doku toksisitesi nedeniyle terapötik kullanımı sınırlıdır. Birçok çalışma, çeşitli dokularda 5-FU'nun neden olduğu hasarın patogenezinde oksidatif stres ve inflamasyonun önemli bir rol oynadığını doğrulamıştır. Doğal bir flavon olan krisin (CHS), antioksidan, anti-inflamatuvar ve antikanser de dahil olmak üzere çeşitli faydalı aktiviteler sergileyebilmektedir. Bu çalışmanın amacı, sıçanların yumurtalık dokusunda 5-FU ile indüklenen oksidatif stres ve inflamasyona karşı CHS'nin terapötik etkisini ilk kez belirlemekti. Otuz adet dişi sıçan kontrol, 5-FU (100 mg/kg), 5-FU+CHS (1 mg/kg), 5-FU+CHS (2 mg/kg) ve CHS (2 mg/kg) olmak üzere 5 gruba ayrıldı. İlk gün intraperitoneal (i.p.) 5-FU tedavisi, takip eden 3 gün CHS (i.p.) uygulandı. Yumurtalık dokularında malondialdehit (MDA), toplam oksidan durum (TOS), toplam antioksidan durum (TAS), 8-hidroksi-2'-deoksiguanozin (8-OHdG), katalaz (CAT) ve interlökin-6 (IL-6) seviyeleri spektrofotometrik yöntemlerle belirlendi. 5-FU grubunda kontrol grubuna göre MDA, TOS, 8-OHdG ve IL-6 düzeyleri anlamlı olarak yüksek iken ($p<0,05$), TAS ve CAT düzeyleri ise istatistiksel olarak anlamlı düzeyde düşüktü ($p<0,05$). CHS tedavileri, oksidatif stres ve inflamasyon parametrelerinin seviyelerini doza bağlı bir şekilde istatistiksel olarak anlamlı derecede düzeltti ($p<0,05$). Sonuçlarımız, CHS'nin 5-FU ile indüklenen yumurtalık hasarına karşı terapötik bir etkiye sahip olabileceğini ve bu nedenle kemoterapiden sonra CHS kullanımının 5-FU ile indüklenen üreme toksisitesini ortadan kaldırmada faydalı olabileceğini düşündürmektedir.

Anahtar Kelimeler: 5-florourasil, İnflamasyon, Krisin, Oksidatif stress, Rat, Yumurtalık hasarı

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INTRODUCTION

Cancer is a disease characterized by the uncontrolled growth and proliferation of abnormal cells and an important public health problem worldwide.[1] Chemotherapy is one of the most widely used methods of cancer treatment.[2] 5-fluorouracil (5-FU) is a widely used antineoplastic agent in the treatment of breast, gastrointestinal, head and neck cancers. The anticancer effect of 5-FU is due its inhibition of thymidylate synthase enzyme, which is responsible for DNA and RNA synthesis in cancer cells.[3] However, 5-FU not only kills cancer cells, but also acts on rapidly dividing normal cells, causing side effects as with other chemotherapeutics.[4] Common intolerable and serious side effects of 5-FU-based chemotherapy are mucositis, hepatorenal toxicity, diarrhea, myelosuppression, cardiotoxicity, dermatitis and reproductive toxicity.[5] These toxic effects of 5-FU limit its clinical use.[4] Since 5-FU is generally used in combination with other chemotherapeutics, information about its harmful effects on the ovaries is limited.[6] However, experimental studies have revealed that 5-FU administration causes ovarian dysfunction, decreased reproductive hormones and follicle numbers in rodents in recent years.[6-8] It has been suggested that 5-FU-induced tissue toxicity is associated with increased oxidative stress and inflammation due to increased formation of reactive oxygen species (ROS), lipid peroxidation and decreased glutathione levels.[9,10] It is therefore suggested that post-chemotherapy undesirable effects in the body can be eliminated by the treatment of chemopreventive agents with antioxidant and anti-inflammatory effects.[11]

Flavonoids are secondary metabolites found in natural products, especially plants, and are phytochemicals that have an important place in the human diet.[12] Chrysin (CHS, 5,7-dihydroxyflavone) is a phytochemical belonging to the flavonoid class, plants containing CHS has been used in traditional medicine since ancient times. CHS has been shown to be one of the main ingredients of some medicinal plants, fruits, mushrooms, honey and propolis.[13] CHS has wide variety of pharmacological activities, including antioxidant, anti-allergic, anti-asthmatic, anti-aging, antihypertensive, antimicrobial, hepatoprotective, neuroprotective, cardioprotective, renoprotective, anti-inflammatory, anticancer, anti-angiogenesis, antihyperlipidemic and antidiabetic.[14,15] There are increasing evidences that CHS reduce the toxicity of various chemotherapeutic agents, such as cyclophosphamide[2], cisplatin[16], 5-FU[17], methotrexate[18] and doxorubicin[19] in different tissues through its antioxidant and anti-inflammatory potential. Although the protection of female reproductive health against 5-FU toxicity in chemotherapy is crucial for the maintenance of fertility, to our knowledge, there are no studies of the therapeutic effect of CHS on 5-FU-induced ovarian damage in an experimental rat model. The aim of this study was therefore to examine whether CHS has a therapeutic effect against 5-FU-induced ovotoxicity within the framework of oxidative stress and inflammation, for the first time.

METHODS

Chemicals

Phosphate buffered saline (PBS) tablet, phosphoric acid, thiobarbituric acid, 1,1,3,3-tetramethoxypropane, sodium carbonate, dimethyl sulfoxide (DMSO), 5-FU and CHS were purchased from Sigma-Aldrich (St. Louis, MO, USA). All reagents used were of analytical grade and of the highest purity.

Animals

The thirty female Sprague-Dawley rats (150±15 g) were obtained from Surgical Practice Research Center of Karadeniz Technical University (Trabzon, Turkey). Rats were housed at room temperature (25°C) with 12 h light/dark cycles and free access to standard pellet diet and tap water. Animals received humane care in accordance with the guidelines of the US National Institutes of Health and prior permission was sought from the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol No: 2021/66). Before treatment, rats were allowed to acclimate for 7 days. The estrus stages of the rats were determined using staining the vaginal smear sample according to the Papanicolaou staining procedure and examining the cell types under the microscope, and only rats whose estrus stage was confirmed were included in the study.[20]

Experimental design

After the familiarization period, the rats were randomly divided into 5 groups with 6 animals in each group. The rats of Group I (control) received physiological saline in first day and DMSO for three consecutive days. The rats of Group II (5-FU) received 5-FU (100 mg/kg) in first day and DMSO for three consecutive days. The rats of Group III and IV (5-FU+CHS groups) received 5-FU

(100 mg/kg) in first day and CHS (1 and 2 mg/kg) for three consecutive days, respectively. The rats of Group V (CHS *per se*) received physiological saline in first day and CHS (2 mg/kg) for three consecutive days. 5-FU and CHS were dissolved in physiological saline and DMSO, respectively. All drugs were administered intraperitoneally (i.p.). Doses of 5-FU[21,22] and CHS[20,23] were selected based on previous studies. The animals were fasted overnight after the final treatment and sacrificed by cervical dislocation on the 5th day, after which the ovaries were removed from the animals in each group.[24] The ovarium tissues were excised and stored at -80℃ for subsequent biochemical analysis.

Biochemical analysis

The tissue samples were homogenized at 9500 rpm in 2 mL of PBS using a homogenizer (IKA, T25 Ultra-Turrax, Staufen, Germany). The supernatant portions were separated by means of centrifugation at 1800xg for 10 min at 4°C and used in the biochemical analysis. Protein levels of the supernatants were determined using a commercial kit (Pierce BCA Protein Assay Kit, Thermo Scientific, Rockford, IL) according to the manufacturer's instructions and calculated as mg/mL bovine serum albumin equivalent. All biochemical parameters measured in the supernatants were proportioned to the amount of protein and expressed as per mg protein.

Malondialdehyde (MDA) levels of tissue samples were determined according to the method developed by Mihara and Uchiyama.[25] 1,1,3,3-tetramethoxypropane was used as a standard and tissue MDA levels were expressed as nmol/mg protein.

Tissue total oxidant status (TOS) and total antioxidant status (TAS) levels were determined using commercial colorimetric kits (Rel Assay Diagnostics, Gaziantep, Turkey) according to the manufacturer's recommendations. The TOS/TAS ratio was used as the oxidative stress index (OSI) and was calculated using the formula[26]:

$$\text{OSI (arbitrary unit)} = \frac{\text{TOS (μmoL hydrogen peroxide equivalent/L)}}{\text{TAS (μmoL trolox equivalent/L)}} \text{ x } 100$$

Tissue catalase (CAT), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and interleukin-6 (IL-6) levels were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (Fine Biotech Co. Ltd, Wuhan, China) according to the manufacturer's recommendations. CAT, 8-OHdG and IL-6 levels were expressed mIU/mg protein, ng/mg protein and pg/mg protein, respectively.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (Version 23.0, NY, USA). The compliance of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. Comparisons of the groups were carried out using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. Statistical significance was set at $p<0.05$.

RESULTS

As shown in Table 1, there were significant increase in the levels of MDA, TOS, OSI, 8-OHdG and IL-6 in the 5-FU-treated group compared with the control group ($p=0.016$, $p=0.0001$, $p=0.0001$, $p=0.0001$ and $p=0.0001$, respectively). Treatment with CHS (1 mg/kg) decreased only the levels of TOS, OSI, 8-OHdG and IL-6 compared with only 5-FU-treated rats ($p=0.0001$, $p=0.0001$, $p=0.045$ and $p=0.002$, respectively). However, there were marked reductions in MDA, TOS, OSI, 8-OHdG and IL-6 levels in case of group treated with CHS (2 mg/kg) as compared to the only 5-FU-treated group ($p=0.033$, $p=0.0001$, $p=0.0001$, $p=0.0001$ and $p=0.0001$, respectively).

The TAS and CAT levels were significantly depleted in the 5-FU-treated group compared to the control group ($p=0.027$ and $p=0.001$, respectively). However, the TAS and CAT levels in the CHS (2 mg/kg)-treated group were significantly increased as compared to the only 5-FU-treated group ($p=0.033$ and $p=0.006$, respectively).

In additon, treatment with CHS (2 mg/kg) alone did not show any significant change in the any biochemical parameter levels compared with the control group ($p>0.05$) (Table 1).

Table 1. Comparison of the levels of biochemical parameters of all experimental groups

	Control	5-FU	5-FU+CHS (1 mg/kg)	5-FU+CHS (2 mg/kg)	CHS (2 mg/kg)
MDA (nmol/mg protein)	29.3±9.3	75.9±41.9[a]	45.3±23.4	33.5±17.9[b]	25.7±7.9
TOS (μM H_2O_2 equivalent/L)	10.8±1.6	58.3±14.1[a]	23.2±13.5[b]	11.1±1.7[b]	11.1±4.3
TAS (mM trolox equivalent/L)	0.93±0.37	0.30±0.13[a]	0.63±0.32	0.92±0.42[b]	0.95±0.39
OSI (arbitrary unit)	1.3±0.5	24.8±9.9[a]	3.8±1.0[b]	1.5±0.8[b]	1.3±0.6
8-OHdG (ng/mg protein)	20.5±19.4	100.9±27.2[a]	70.2±14.3[a,b]	22.6±12.5[b,c]	22.9±10.5
CAT (mIU/mg protein)	142.5±26.0	71.1±18.5[a]	109.1±25.0[a]	128.8±24.4	135.4±32.7
IL-6 (pg/mg protein)	111.8±33.1	432.4±155.7[a]	224.5±98.0[b]	117.9±21.7[b]	118.6±21.5

5-FU: 5-fluorouracil, CHS: chrysin, MDA: malondialdehyde, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, 8-OHdG: 8-hydroxy-2'-deoxyguanosine, CAT: catalase, IL-6: interleukin-6.
P-values according to one-way ANOVA test, post-hoc Tukey test. Data were expressed as mean±SD.
[a]p<0.05 compared with control group,
[b]p<0.05 compared with 5-FU group.
[c]p<0.05 compared with 5-FU+CHS (1 mg/kg) group.

DISCUSSION

Ideal chemotherapy aims to cause minimal damage to healthy cells while killing cancerous cells. However, there is no chemotherapy protocol that does not harm healthy cells at all in practice.[6] 5-FU is one of the most widely used chemotherapeutics in the world, and ovarian tissue is one of the tissues most affected by 5-FU chemotherapy.[8] 5-FU-induced tissue toxicity is a complex and multistage phenomenon. It involves a number of pathological processes, such as overproduction of ROS, alteration of various signaling pathways and increased inflammation. It is therefore suggested that the use of agents with antioxidant and anti-inflammatory potential may be beneficial in eliminating 5-FU-related tissue toxicity.[5] This study therefore aimed to evaluate the therapeutic efficacy of CHS against 5-FU-induced ovarian damage for the first time.

5-FU-induced lipid peroxidation and free radical generation leading to cell membrane damage are considered as the main mechanism behind its toxic effects.[11] MDA is a lipid peroxidation end product and accepted as a direct indicator of the degree of oxidative stress.[12] It is well known that two of the crucial parameters for evaluating redox balance in biological systems are TAS and TOS. While TAS determines the overall ROS scavenging ability in a biological sample, TOS can be defined as the cumulative amount of total oxidants in the sample. For the quantitative assessment of redox homeostasis disorders, the OSI, which is called the "gold indicator of oxidative stress", is used.[27] Oxidative stress also increases DNA damage and 8-OHdG is one of the main products of DNA oxidation.[28] The increased MDA, TOS, OSI and 8-OHdG levels and decreased TAS levels in 5-FU-treated rats indicates that 5-FU toxicity is mediated by ROS-induced oxidative cell damage. These findings are consistent with data from previous studies demonstrating that 5-FU increases oxidative stress and DNA damage.[4,5,10] CHS treatments restored these levels in a dose-dependent manner. The alleviation of oxidative stress and DNA damage parameters by CHS treatments with may be due to the free radical scavenging potential of CHS.[14,15] Similar with our results, CHS has previously been shown to prevent chemotherapeutic-induced tissue damage by inhibiting the levels of oxidative stress and DNA damage in experimental models.[11,16,18,19]

Removal of free radicals in biological systems is achieved through enzymatic and non-enzymatic antioxidants, which act as the main defense systems against free radicals.[12,20] CAT is the enzyme with the highest known turnover number and catalyzes the reduction of hydrogen peroxide to water.[28] The findings showed that systemic administration of 5-FU suppressed CAT levels in ovarian tissue. It can be said that this situation may have made the ovarian tissue more prone to 5-FU-induced damage. This is consistent with the results of previous experimental studies on 5-FU-induced tissue damage.[11,29,30] However, treatments with CHS significantly increased the levels of CAT in a dose-dependent manner. Similarly, CHS has previously been shown to prevent chemotherapeutic-induced tissue damage by increasing the levels of antioxidant enzymes in various experimental models.[31-33]

Oxidative stress and inflammatory processes are closely related and pro-inflammatory cytokines play an important role in chemical-induced acute tissue

injury.[34] Increasing evidences point to the role of increased inflammation in 5-FU-induced tissue damage.[5,11,35] IL-6 is a very important cytokine involved in the pro-inflammatory process and there is a positive correlation between increased IL-6 levels and the degree of inflammation.[2,36] Our findings revealed that higher IL-6 levels appeared in the ovarian tissue of rats exposed only to 5-FU than control group and CHS treatments significantly reduced these values in a dose-dependent manner. This improvement appears to be due to the anti-inflammatory property of CHS, which has often been demonstrated.[14,15] Consistent with our results, CHS has previously been shown to prevent chemotherapeutic-induced tissue damage by inhibiting inflammation in experimental models.[2,32,33]

Flavonoids are secondary metabolites originating from natural products and it is suggested that regular and balanced intake of flavonoids is associated with a lower risk of cancer, neurodegenerative and cardiovascular diseases.[12] The antioxidant activities of flavonoids are due their ability to scavenge free radicals, chelate metal ions, and modulate antioxidant enzymes.[33] CHS is a popular member of the flavonoid family, and its antioxidant activity has been reported to be mainly due to the hydroxyl and keto groups in its rings.[37] Therefore, it is thought that the therapeutic effect of CHS on 5-FU-induced ovarian damage is mainly due to its antioxidant properties.

CONCLUSION

CHS could attenuate 5-FU-induced ovarian toxicity by decreasing oxidative stress and inflammation and increasing antioxidant status. This study supports the hypothesis that CHS is a potential therapeutic compound that can be used for the alleviation of 5-FU-induced ovarian injury.

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Authorship contribution statement

Consept and desing: EAD.

Acquisition of data: EAD, HK, SD and NTA

Analysis and interpretation of data: EAD, AM, SD and YA.

Drafting of the manuscript: EAD and SD.

Critical revision of the manuscript for important intellectual content: YA.

Statistical analysis: AM.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study was approved by the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol no: 2021/66) and performed according to the animal research reporting of *in vivo* experiments (ARRIVE) guidelines.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Investigation of The Effects of Endogenous BDNF on Kainic Acid Induced Seizures

Endojen BDNF'nin Kainik Asit Kaynaklı Nöbetler Üzerindeki Etkilerinin İncelenmesi

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ABSTRACT

Brain derived neurotrophic factor (BDNF), a major mediator of plasticity in the central nervous system. Due to fast synaptic actions of BDNF, it is thought to be a modulator of excitability in neuronal circuitry. There is a two sided relationship between BDNF and epileptic activity. BDNF levels increase following seizure or kainate administration. Additionally, BDNF administration causes hyperexcitability. BDNF deficiency attenuates seizures or epileptiform activity in several epilepsy models. In this study, our aim was to investigate modulatory effects of reduced endogenous BDNF on kainic acid (KA) induced seizures. For this purpose, BDNF heterozygous mice and their wild type littermates were compared. Animals were injected intraperitoneally with either vehicle (0.9% saline) or kainic acid (15 mg/kg). Four groups were formed: vehicle (saline, SA) injected wild type (SA-WT; n=9) and BDNF heterozygous mice (SA-HT; n=9), kainic acid injected wild type (KA-WT, n=10) and BDNF heterozygous mice (KA-HT, n=10). Racine scorings were determined for 5 min epochs from the video recordings. In the hippocampal tissue synaptic markers proteins synaptophysin (SYP), post-synaptic density (PSD-95) and inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor Alpha (TNF-α) were measured. Besides, oxidative stress parameters were evaluated. KA-WT group's score were higher at 20 and 25 min than that of KA-HT group ($p<0.05$). MDA levels were higher in kainic groups ($p<0.05$). Kainic acid did not affect neuroinflammation and synaptic proteins significantly. Our results showed that reduced BDNF temporarily posed a resistance against seizure but intact levels of BDNF failed to protect against oxidative stress in kainic acid model.

Keywords: BDNF, Kainic acid, Epilepsy, Synaptic proteins, Oxidative stress

ÖZET

Beyin kaynaklı nörotrofik faktör (BDNF), merkezi sinir sisteminde plastisitede rol oynayan önemli bir peptittir. BDNF'nin hızlı sinaptik etkileri nedeniyle, nöronal devrede uyarılabilirliği düzenlediği düşünülmektedir. BDNF ile epileptik aktivite arasında iki yönlü bir ilişki vardır. Nöbet veya kainat uygulamasını takiben BDNF seviyeleri yükselir. Bunun yanında, BDNF uygulaması aşırı uyarılabilirliğe neden olur. BDNF eksikliği, birkaç epilepsi modelinde nöbetleri veya epileptiform aktiviteyi azaltır. Bu çalışmada amacımız, azaltılmış endojen BDNF'nin kainik asit (KA) kaynaklı nöbetler üzerindeki modülatör etkilerini araştırmaktı. Bu amaçla BDNF heterozigot fareler ve bunların yabani tip kardeşleri karşılaştırıldı. Hayvanlara %0.9'luk tuzlu su çözeltisi veya kainik asit (15 mg/kg) intraperitoneal olarak verildi. Dört grup oluşturuldu: tuzlu su (saline, SA) enjekte edilen yabani tip fareler (SA-WT; n=9) ve BDNF heterozigot fareler (SA-HT; n=9), kainik asit enjekte edilen yabani tip (KA-WT, n=10) ve BDNF heterozigot fareler (KA-HT, n=10). Video kayıtlarından 5 dakikalık periyotlarla 120 dakika boyunca Racine skorları belirlendi. Hipokampal dokuda, sinaptik proteinler sinaptofizin (SYP) ve PSD-95'in yanında inflamatuar belirteçler interlökin-6 (IL-6) ve tümör nekroz faktörü alfa (TNF-α) ölçüldü. Ayrıca oksidatif stres parametreleri değerlendirildi. KA-WT grubunun skoru 20 ve 25. dakikada KA-HT grubuna göre daha yüksekti ($p<0.05$). MDA düzeyleri kainik gruplarda daha yüksekti ($p<0.05$). Kainik asit, nöroinflamasyonu ve sinaptik proteinleri önemli ölçüde etkilemedi. Sonuçlarımız, azalmış BDNF'nin geçici olarak nöbete karşı bir direnç oluşturduğunu, ancak normal BDNF düzeylerinin kainik asit modelinde oksidatif strese karşı koruma sağlamadığını gösterdi.

Anahtar Kelimeler: BDNF, Kainik asit, Epilepsi, Sinaptik proteinler, Oksidatif stres

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INTRODUCTION

Brain derived neurotrophic factor (BDNF), a member of neurotrophin family is widely distributed in the central nervous system, with the highest expression levels in the hippocampus and cortex which are involved in learning, memory, excitability and plasticity.[1,2] Relevant to its trophic roles, BDNF is required for normal functional development of neuronal structures, maturation and maintenance of synaptic transmission. However, BDNF changes the synaptic transmission within minutes.[3] BDNF exerts its neuronal roles both in presynaptic and postsynaptic functions. Presynaptic actions of BDNF is to increase glutamate release, phosphorylate synapsin, a presynaptic protein that is involved in synaptic transmission[4], and postsynaptically BDNF phosphorylate NMDA receptors.[5] Thus, BDNF may be an endogenous modulator of excitability in adult brain. Studies have shown that the level of BDNF protein increased after kindling[6] and kainate administration.[7] Exposure to exogenous BDNF can lead to hyperexcitability in cultures[8] and in brain.[7] In line with this hypothesis, kindling was prevented in BDNF knockout mice[9]. Besides, BDNF heterozygous mice were slightly more resistant to an experimental focal epilepsy model and reduced Gamma band activity in their Ecog recordings.[10] On the other hand, in transgenic mice overexpressing BDNF, seizures in response to kainic acid were more severe and even spontaneous seizures were observed in some animals.[11] However, the alterations in BDNF levels in response to epileptic insults may be a protective action of BDNF. Indeed, some studies suggest exogenous BDNF has a protective action in epilepsy.[12-14] As can be seen, there are conflicting results in the literature on BDNF and epilepsy. Apart from its roles as a neurotrophic factor and a neuromodulator peptide, BDNF more lately shown to act as a supporting factor of antioxidant systems[15] and contributes to anti-inflammatory mechanisms in the central nervous system.[16] In fact BDNF heterozygous mice have been shown to have higher inflammation and higher oxidative stress in the brain tissues.[17] Systemic administration of kainic acid (KA) induces epileptic seizures and neuroexcitotoxicity in animal models.[18] KA binds to kainate receptors which are ionotropic non-NMDA (N-methyl-D-aspartate) glutamate receptors. KA activates glutamate receptors and this over stimulation of glutamate receptors causes influx of calcium ions, production of superoxide radicals, and mitochondrial dysfunction leading to neuronal apoptosis and necrosis.[19] Administration of kainic acid leads to seizures[20], behavioral changes[21], oxidative stress[22], and inflammatory responses.[23,24] Although these effects of KA are well known, effects on synaptic proteins responsible for synaptic vesicular trafficking are not known. The concentrations of synaptic proteins are directly related to the neuronal function and we wanted to test whether kainic acid induces any changes in synaptic protein levels. In this study, our aim was to define the seizure severity of BDNF heterozygous mice in kainic acid model of epilepsy. Besides, we investigated the possible protective role of BDNF against kainic acid induced inflammation and synaptotoxicity.

METHODS

Animals

The study was approved by Karadeniz Technical University Animal Care and Ethics Committee (approval number: 2017/38). All experimental procedures were performed in Karadeniz Technical University Surgical Application and Research Center. Male BDNF heterozygous and their wild type litter mates were used in this study. In total 38 male mice aging 5-6 months weighing 20-25 g housed 3-4 animals per cage under regulated temperature and humidity in the 12 h light-dark cycle. BDNF heterozygous mouse model used in the present study was established by Korte and coworkers.[25] Heterozygous knockout model is characterized by one missing allele of the BDNF coding region. This allele was replaced by NEO, a neomycine-resistance gene. BDNF heterozygous mice (BDNF (+/−)) are viable and fertile. Mice are produced by crossing a male BDNF (+/-) with a normal wild-type female mouse, BDNF (+/+). The phonotypes of wild-type and heterozygous age matched male mice were compared for the study. To determine the genotype of the mice, the presence of the NEO was verified by polymerase chain reaction (PCR). The tissue for genotyping was collected from tail tissue. Animals were randomly divided into four groups. All animals were injected intraperitoneally (ip) with either vehicle (0.9% saline) or kainic acid at a dose of 15 mg/kg body weight. The groups were vehicle injected wild type (SA-WT) and BDNF heterozygous mice (SA-HT), kainic acid injected wild type (KA-WT) and BDNF heterozygous mice (KA-HT). Injections were made in the morning

between 9:00 and 9:30 as a single dose. After 24 hours from injection, animals were decapitated and brains were removed and dissected to separate right and left cortices and hippocampus. Until the biochemical analysis the tissues were stored at -80 °C.

Behavioral Seizures

Behavioral observations were recorded for 120 min after vehicle or kainic acid injections. Each animal was placed in a plastic cage separately and video recordings were made to verify neurological effects. Onset of seizure latency and seizure incidence were measured offline. Racine scoring[26,27] were used to assess convulsive behavior. Score 0: no abnormal behavior; Score 1: freezing briefly, staying immobile; Score 2: facial and whisker automatism; Score 3: clonic head bobbing; Score 4: forelimb clonus; Score 5: clonic rearing; Score 6: generalized seizures: shivering, falling and jumping. Scores 1–4 were accepted as low-grade or mild seizures. Scores 5–6 are accepted as high-grade or severe seizures. The behavioral experiments were recorded to a personal computer by using a camera. The analysis was made offline. During the analysis and scoring, the researcher was blinded to group or number of the animals.

Enzyme-linked immunosorbent assay (ELISA)

ELISA was used for the determination of cortical concentration of synaptophysin protein (SYP) and postsynaptic density 95 kD (PSD-95) protein and the levels of neuroinflammation markers IL-6 and TNF-α. For ELISA measurement, left cortex of each mouse were separated and processed. Lysis buffer (1 mg/tissue weight) contained: 137 mM NaCl, 2.7 mM KCl, 1.5 mM KH_2PO_4, 7.7 mM Na_2HPO_4, 1% Triton X-100, 5 mg/mL aprotinin, 5 mg/mL leupeptin m, pH 7.4. Then the cortical tissue was homogenized by an ultrasonic cell disrupter (Sonics vibracell, Newtown, CT, USA) and the suspension was centrifuged at 20,000 x g for 20 min. The supernatant was used for ELISA tests. TNF-α, IL-6, SYP and PSD-95 levels were determined by using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, Catalog No: E-EL-M0049, E-ELM0044, E-EL-M1105 and USCN, Catalog No: SEG168Mu, respectively) according to the manufacturer's guide. Samples and standards absorbance were measured at 450 nm by using tunable microplate reader (VERSA max, Molecular Devices, Sunnyvale, CA, USA). Results were expressed as ng/mL.

Tissue malondialdehyde (MDA) measurement

Right cortex of the mice was used for oxidative stress parameters. Tissue was homogenized in 2 mL ice-cold buffer 1.15% KCl solution containing 0.5 mL/L Triton X-100. MDA concentrations were measured from homogenates according to method by Mihara and Uchiyama.[28] Tetramethoxypropane was used as standard solution. MDA levels were expressed as nmol/ml per gram of wet tissue.

Measurements of tissue antioxidant enzyme activities

For measurement of superoxide dismutase (SOD) and catalase (CAT) activities, tissues were homogenized in 2 ml ice-cold Tris-HCl buffer (50 mmol/L, pH = 7.4). SOD activities were measured by the method of Sun et al.[29] This method essentially is based on reduction of nitroblue tetrazolium by xanthine/xanthine oxidase system. SOD activity was given in U/mg protein. CAT activities were determined by the method of Goth.[30] This method utilizes H_2O_2 and ammonium molybdate stable complex. The yellow complex was measured at 405 nm. CAT activities were expressed as kU/mg protein. For determination of protein concentrations, the tissue lysates were used. Bicinchoninic acid protein assay kit was used (Merck Millipore, Darmstadt, Germany) and results were expressed as mg/mL.

Statistical analysis

5 min Racine scores were compared between KA-WT and KA-HT groups by using paired t test. One way ANOVA was used for the statistical analysis of biochemical data of each group. For multiple comparisons Tukey's post hoc test was used. All the statistical tests were performed by using GraphPad Prism software. Data were presented as means ± SEM. For the significance $p < 0.05$ was accepted.

RESULTS

Behavioral seizure

All mice that injected kainic acid (KA) were observed and video recorded for 2 hours. Racine scorings were determined for 5 min epochs from the video recordings. The wild type or heterozygous mice received saline (SA-WT and SA-HT groups) did not exhibit any seizure like behavior. Hence their scores were 0 for all time epochs. Their scores also removed from the graph. The other two groups received kainic acid injections and developed seizures which were eminent from the behaviors. There were no significant differences in onset of seizure latency between two groups. Racine scores were significantly different between KA-WT and KA-HT group only in two 5 min epoch that are 20 and

25 min ($p<0.05$) (Figure 1). KA-WT group's score were higher at this time points than that of KA-HT group. At these time points, the seizures were more severe in wild type than BDNF heterozygous animals.

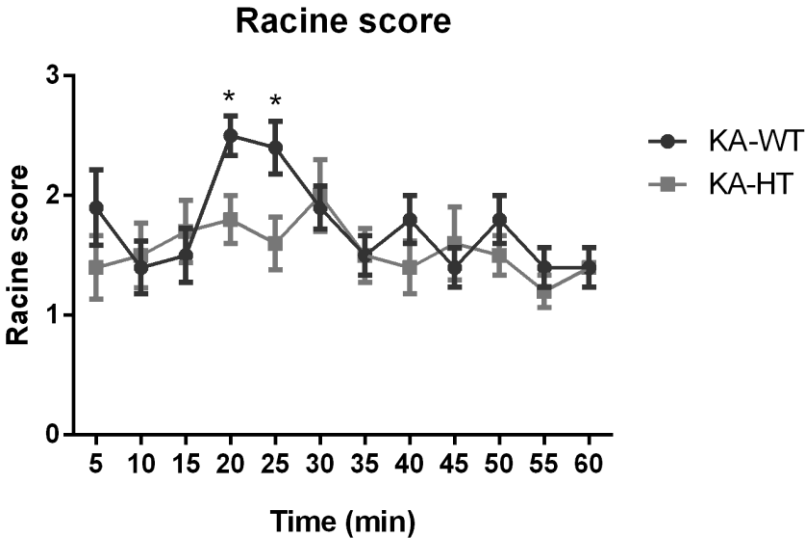

Figure 1. Seizure severity of the mice were evaluated according to Racine Scorings. The mice received kainic adic injections showed epileptic seizures. The seizure of BDNF heterozygous mice (KA-HT) were significantly milder than wild types (KA-WT) after 20 to 25 minutes kainic adic injections (*: $p<0.05$). The control groups for this experiment received saline and did not showed any epileptic behavior. The scores of all the mice in saline groups (SA-WT and SA-HT) were zero and were not included in the graph.

Oxidative Stress Neuroinflammation

To search the effects of KA injection on oxidative stress parameters were measured brain MDA level, SOD and CAT activity. MDA levels were significantly different between groups according to one way ANOVA test ($F(3.34) = 10.82$, $P < 0.0001$). MDA levels were importantly higher in KA-WT and KA-HT compared to SA-WT groups according to Tukey's post hoc test ($p=0.0075$ for KA-WT group and $p=0.0004$ for KA-HT group). MDA levels in the groups that received KA were also significantly higher than that of SA-HT group ($p=0.0082$ for KA-WT group and $p=0.0005$ for KA-HT group). MDA levels of all groups were shown in Figure 2A. One way ANOVA showed no significance in SOD ($F(3.34) = 1.793$, $p> 0.05$) and CAT activities ($F(3.34) = 1.952$, $p>0.05$) between groups (Figures 2B and 2C).

Neuroinflammation

The effects of KA injection to wild type and BDNF heterozygous mice on neuroinflammation were investigated by measuring the levels of cortical levels of interleukins (IL-6β) and tumor necrosis factors (TNF-α). Statistical analysis displayed no significance in IL-6β ($F(3.34=0.766$, $p>0.05$) and TNF- α ($F(3.34)=1.343$, $p>0.05$) differences between the groups (Figure 3A and 3B).

Synaptic Proteins

In this study, KA administration to mice did not affect the synaptophysin protein (SYP) and postsynaptic density 95 kD (PSD-95) protein levels. One way ANOVA revealed no significant differences in synaptic proteins between the groups ($F(3.34)= 0.371$, $p>0.05$ for SYP; $F(3.34)=0.216$, $p>0.05$). The levels of synaptic proteins are shown in Figure 4A and 4B.

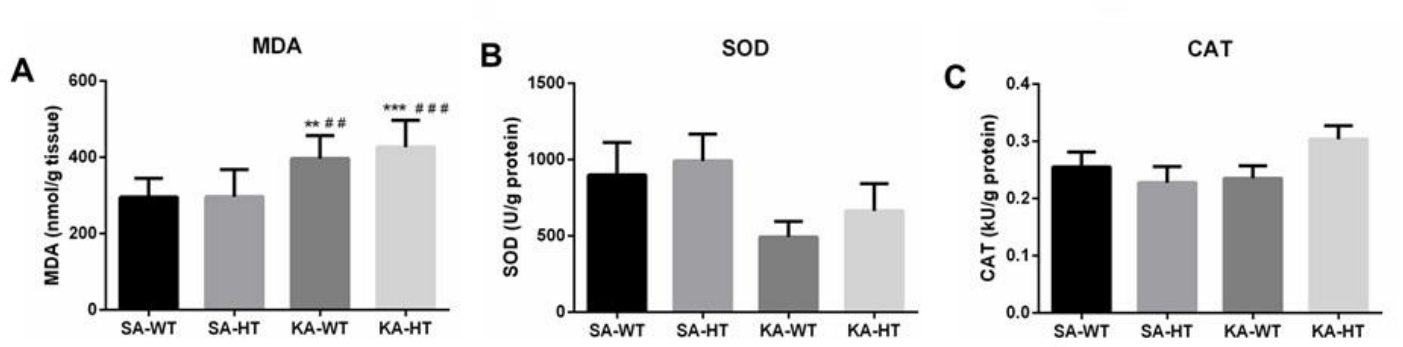

Figure 2. Oxidative stress parameters measured in the hippocampus tissues are shown. BDNF concentration did not affect the oxidative stress parameters. A. Kainic acid significantly increased MDA levels. MDA levels of KA-WT group (##: p< 0.01 , **: p< 0.01) and KA-HT group were higher than the SA-WT and SA-HT groups (###: p<0,001, ***: p< 0.001) B and C show the SOD and CAT activity in the hippocampal tissue homogenates. Antioxidant enzymes were not changed after kainic acid administration.

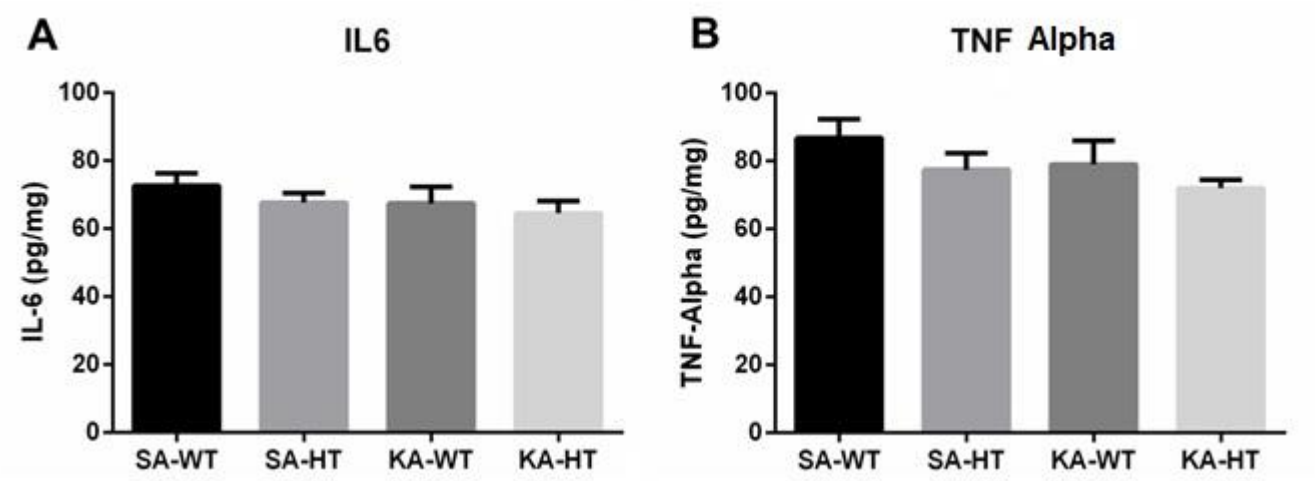

Figure 3. IL-6 and TNF alpha levels were measured in the hippocampus. Inflammation markers showed no change following kainic acid administration. In the hippocampus tissues of BDNF heterozygous mice, inflammation markers were not different than the wild type group.

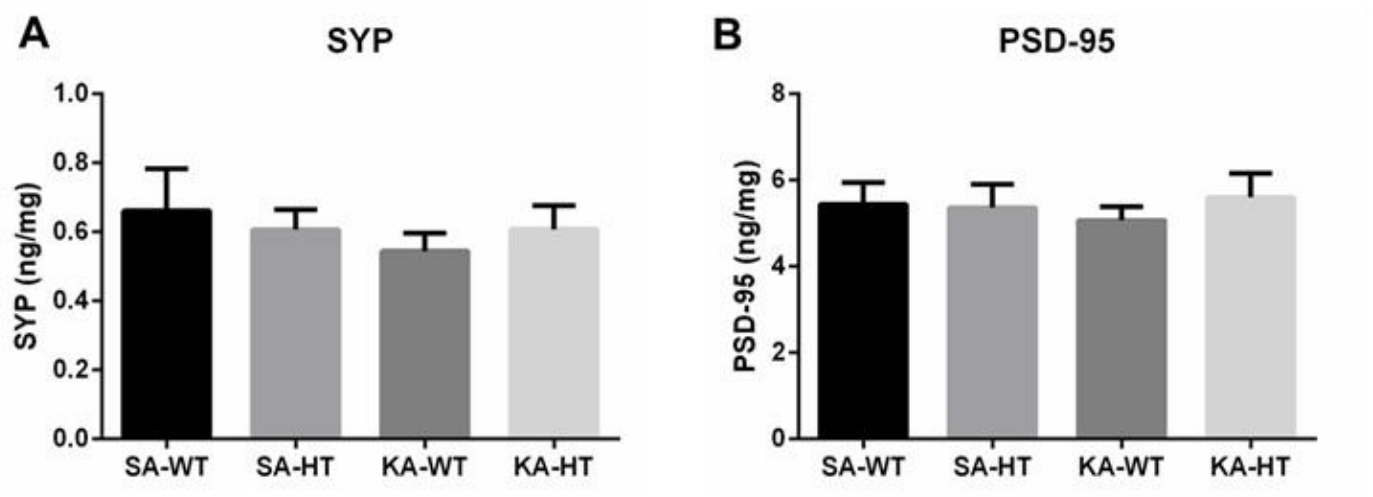

Figure 4. As a biochemical correlate of behavior and possible loss of function, synaptic protein levels measured in the hippocampus tissues. A typical presynaptic protein (synaptophysin (SYP)) and a postsynaptic protein (postsynaptic density 95 kD (PSD-95)) has been chosen and measured by ELISA. SYP and PSD-95 concentrations in the hippocampus tissues were not altered.

DISCUSSION

Since its discovery, BDNF is essentially considered as a neurotropic factor that is pivotal for the adaptive long-term changes in the central nervous system. Yet, it has been proposed that BDNF acts as a neuroprotective, anti-inflammatory and antioxidant properties as well. Kainic acid binds to kainat receptors which are ionotropic glutamate receptors and leads to potent excitatory post synaptic currents. This unusual strong activation of kainat receptors results in unbalanced excitation which in turn triggers seizures. Sustained activity also results in oxidative damage, inflammation and loss of neuronal function.[19,22,23] In the present study, we aimed to reveal the role BDNF on the severity of kainic acid induced seizures. Besides, we investigated whether BDNF poses a protective role against kainic acid induced changes in the hippocampus. Our data showed i) BDNF heterozygous mice slightly more resistant to kainic acid induced seizure. ii) Kainic acid application increased the lipid peroxidation but had no effect of synaptic proteins and inflammation markers. BDNF heterozygous mice lack one BDNF coding alleles in their genome and in the brain these mice express nearly %40-50 lower levels of BDNF.[31] It has been a useful model to study the physiological roles of BDNF since the heterozygous mice did not show abnormal phenotype.[32,33] The epileptic phenotype of BDNF heterozygous mice has been investigated in different experimental models. In a kindling model BDNF heterozygous mice more resistant[9] and in an electrically induced seizure model, BDNF heterozygous mice did not differ from the wild type littermates.[34] In another study, similar to present findings BDNF heterozygous mice showed reduced frequency of electrical discharges in their electro-corticogram activities in a focally induced epilepsy model.[10] Apart from the above mentioned findings, in the present study, for the first time we showed that, in kainic acid model too, BDNF heterozygous mice were slightly more resistant to epileptic seizures. This finding of ours is in line with the previous reports. In general, the BDNF/Trk-B signaling favors the excitation and disrupted Trk-B signaling reduced the excitation.[35,36] In kainic acid model, we can argue that, reduced levels of BDNF in hippocampus led to suppressed levels of excitability which eventually resulted in a less severe epileptic seizure. Epileptic seizures often lead to elevated inflammation and oxidative stress in the brain. In this study, we also tested whether BDNF has an antiinflammation and/or antioxidant role in kainic acid induced seizure model. The relation between BDNF and neuroinflammation in various experimental models of neurological disorders and neurodegenerative diseases are well documented.[37] Studies showed that BDNF had anti-inflammatory effects both in vitro and in vivo[38]. In BDNF heterozygous mice, upon LPS administration, higher inflammation levels were measured compared to wild type.[39] In our study, the kainic acid administration did not lead to increased levels of measured inflammation markers. Hence, we could not evaluate whether BDNF posed a protection against inflammation. We have used the lowest dose of kainic acid (15 mg/kg) to be able to reveal the difference between heterozygous and wild type animals. Higher doses would create a stronger effect in both groups and the hypothesized differences would be lost. Unlike the neuroinflammation markers, lipid peroxidation levels were increased in kainic acid groups. Kainic acid administration increased the MDA levels in hippocampus. BDNF was shown to support the antioxidant systems in various studies.[15,17] However, in the present work, wild type and heterozygous mouse exhibited similar MDA levels, indicating that the reduced BDNF levels did not further exacerbate the lipid peroxidation. This result contradicts with the literature. The model used in this study was different than the other reports. The pathway that kainic acid induced lipid peroxidation might be independent of the BDNF-Trk-B pathway. Neurons are strong cells that are resistant to many challenging conditions. We thought that, following kainic acid administration, there may not be a neuronal loss. However, in such mild to moderately harmful conditions, number of synaptic contacts is lost between the neurons which in turn reduce the performance. The number of functionally active synapses is directly correlated to synaptic proteins. In our study we measured two synaptic proteins: a major presynaptic protein synaptophysin protein (SYP) and a postsynaptic protein postsynaptic density 95 kD (PSD-95). To our knowledge, there is only one study to investigate the effects of KA on synaptic proteins. However, in that study, they investigated the effects of administration of KA to 7 days old (P7) rat on synaptic markers in adulthood (P100). They observed a decrease in two synaptic markers, SNAP-25 and syntaxin.[40] Similar to inflammatory markers, we did not observe any changes in the levels of synaptic proteins. Kainic acid

administration did not result in reduced number of synapses. Higher doses of kainic acid probably could have triggered a stronger seizure and led to loss of synapses.

CONCLUSION

In kainic acid induced seizure model, weakened BDNF signaling led to milder seizures. Slight and transient seizures are associated with increased lipid peroxidation but did not result in increased neuroinflammation. Similarly, synaptic proteins were not affected.

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Authorship contribution statement

Consept and desing: SAA, İA

Acquisition of data: HK, ES.

Analysis and interpretation of data: SAA, İA and AA.

Drafting of the manuscript: SAA, İA.

Critical revision of the manuscript for important intellectual content: İA.

Statistical analysis: SAA.

Supervision: SAA.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study was approved by the Local Animal Research Ethics Committee of Karadeniz Technical University.

Availability of data and materials

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Relationship between in-Hospital Mortality and Renal Dysfunction after Primary Percutaneous Coronary Intervention in Turkish Geriatric Patients with ST-elevation Myocardial Infarction

ST yükselmeli Miyokard İnfarktüslü Türk Geriatrik Hastalarda Primer Perkütan Koroner Girişim Sonrası Hastane içi Mortalite ile Renal Disfonksiyon Arasındaki İlişki

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ABSTRACT

Geriatric population (>80 years) has an increased mortality risk due to several reasons including more extensive coronary artery disease (CAD) and impaired renal function. We investigated the relationship between in-hospital mortality and renal dysfunction in geriatric patients with ST-elevation myocardial infarction (STEMI) who underwent primary percutaneous intervention (PCI). We included 203 geriatric patients with STEMI who underwent primary PCI. Patients were divided into 2 groups; group 1 comprised 42 patients who died in the hospital after MI, and group 2 included 161 patients who were discharged following primary PCI. The risk factors of the patients were determined. We calculated coronary artery disease prevalence by Gensini risk score, renal function by creatinine clearance (CrCl), and compared 2 groups. The patients in group 1 who died in hospital after STEMI were older; they had more extensive CAD and lower CrCl (age: 82 ± 5 yr, 78 ± 7 yr, p<0.001; Gensini score: 70 ± 30, 42 ± 26, p: 0.001; CrCl: 46 ± 17 mL/min, 65 ± 18 mL/min, p<0.001). When multivariate analysis was performed with logistic regression, we found to be CrCl, HDL-cholesterol, and Gensini scores to be the independent predictors of in-hospital mortality (CCL: OR 1.057 (1.029-1.086), p = 0.001); HDL: OR 1.077 (1.021-1.136), p = 0.007, Gensini score: OR 0.969 (0.952-0.985), p = 0.001). Renal dysfunction increases in-hospital mortality in elderly patients with STEMI undergoing primary PCI. Renal dysfunction in elderly patients with MI is an important risk factor that increases in-hospital mortality like other cardiovascular risk factors.

Keywords: Geriatric population, ST elevation myocardial infarction, renal function, creatinine clearance, Gensini score.

ÖZET

Geriatrik popülasyon (>80 yaş), daha yaygın koroner arter hastalığı (KAH) ve bozulmuş böbrek fonksiyonu gibi çeşitli nedenlerden dolayı artmış mortalite riskine sahiptir. Primer perkütan girişim (PCI) uygulanan ST yükselmeli miyokard enfarktüsü (STEMI) olan geriatrik hastalarda hastane içi mortalite ile böbrek fonksiyon bozukluğu arasındaki ilişkiyi araştırdık. Primer PCI uygulanan STEMI'li 203 geriatrik hastayı dahil ettik. Hastalar 2 gruba ayrıldı; grup 1, Miyokard infarktüsü (MI) sonrası hastanede ölen 42 hastadan, grup 2 ise primer PKG sonrası taburcu edilen 161 hastadan oluşuyordu. Hastaların risk faktörleri belirlendi. Koroner arter hastalığı prevalansını Gensini risk skoru ile, renal fonksiyonu kreatinin klirensi (CrCl) ile hesapladık ve 2 grubu karşılaştırdık. Grup 1'de STEMI sonrası hastanede ölen hastalar daha yaşlıydı; daha yaygın KAH ve daha düşük CrCl'ye sahiptiler (yaş: 82 ± 5 yıl, 78 ± 7 yıl, p<0.001; Gensini skoru: 70 ± 30, 42 ± 26, p: 0.001; CrCl: 46 ± 17 mL/dk, 65 ± 18 mL/dak, p<0.001). Lojistik regresyon ile çok değişkenli analiz yapıldığında CrCl, HDL-kolesterol ve Gensini skorlarının hastane içi mortalitenin bağımsız öngördürücüleri olduğunu bulduk (CCL: OR 1.057 (1.029-1.086), p = 0.001); HDL: OR 1.077 (1.021-1.136), p = 0.007, Gensini skoru: OR 0.969 (0.952-0.985), p = 0.001). Primer PKG uygulanan STEMI'li yaşlı hastalarda renal disfonksiyon hastane içi mortaliteyi artırmaktadır. MI'lı yaşlı hastalarda böbrek fonksiyon bozukluğu, diğer kardiyovasküler risk faktörleri gibi hastane içi mortaliteyi artıran önemli bir risk faktörüdür.

Anahtar Kelimeler: Geriatrik popülasyon, ST yükselmeli miyokard infarktüsü, böbrek fonksiyonu, kreatinin klirensi, Gensini skor

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INTRODUCTION

Cardiovascular disease (CVD) is one of the important causes of death in western countries.[1] The risk of cardiovascular disease is high in renal failure.[2-4] It is also known to increase the risk of chronic kidney disease (CKD), myocardial infarction (MI), and cardiovascular mortality.[5,6] Twenty to 50% of patients with acute ST-elevation myocardial infarction (STEMI) are over 65 years of age. More than 60% of deaths due to MI occur in this age group.[7] The frequency of chronic kidney disease increases with age and increases cardiovascular morbidity and mortality due to ventricular arrhythmia, heart failure, which is one of the in-hospital complications.[8]

We investigated the factors associated with in-hospital mortality in elderly patients undergoing primary percutaneous intervention (PCI) for STEMI.

METHODS

Our study is a retrospective study, we included 203 geriatric patients who underwent MI and primary PCI between October 2016 and October 2018.

We received the ethics committee approval of the study at non-interventional clinical studies ethics committee of Recep Tayyip Erdogan University (Local Ethical Committee) (Decision no: 2016/13). Patients were participated in a random and consecutive manner. Forty-two patients died in the hospital and 161 patients were discharged. We identified risk factors for these two groups. Coronary artery disease (CAD) severity was assessed by Gensini risk scoring[9], renal function was assessed by creatinine clearance (CrCl), and two groups were compared. We used logistic regression analysis to determine in-hospital mortality predictors after primary PCI.Acute STEMI was diagnosed as having two of the following three criteria:[10]

1- ST-segment elevation in consecutive ≥2 leads (≥2 mm in chest lead, ≥1 mm in extremity lead). 2- Ischemic chest pain lasting over 30 minutes. 3- Serum creatinine kinase myocardial band (CK-MB) level increased at least two times of normal range. Patients who presented in the subacute period (symptom onset > 12 hours), had MI, 3 months past, or underwent coronary artery bypass graft (CABG) surgery or PCI revascularization, had myocardial infarction from the left main coronary artery, and had emergency CABG surgery were excluded from the study. An informed consent form was signed by all patients. Blood samples required for randomization were taken from the patients by direct venous puncture. Serum creatinine (Cr) and biochemical parameters were analyzed in a standard laboratory using an appropriate method. In the study, the accuracy of the biomarker measurements of the centers and the clinical laboratory measurement were evaluated with a significant quality measure. We used the Cockroft-Gault equation to calculate CrCl as follows: ([{140 - in age} x body weight in kg] / {72 x Cr mg/dL}) x 0.85 (female gender). In our study, according to the age of the patient population, we divided the patients into two groups as CrCl> 45 mL/min and CrCL <45 mL/min. The study was conducted in accordance with the 1975 Helsinki Declaration in accordance with the ethical rules.

Primer Percutaneous Coronary Intervention Procedure: Aspirin (300 mg) and clopidogrel (300 mg) were given orally at emergency, and 100 U / kg (max 10.000 U) heparin was administered after femoral artery puncture. Primary PCI (balloon angioplasty and/or stent implantation) was performed on infarcted arteries after coronary angiography. During the procedure, coronary artery flow (Thrombolysis in Myocardial Infarction (TIMI) classification) was used.[11]

Successful stent angioplasty procedure was considered as achieving less than 20% residual stenosis and TIMI-III flow after stent placement. Recurrent infarction was defined as recurrent cardiac enzyme and ST segment elevation associated with chest pain lasting over 30 minutes after the first 24 hours of infarction. Major bleeding was defined as hemorrhage causing a decrease in hemoglobin level > 5 g/dL or any grade of intracranial hemorrhage. We made comparisons between groups in terms of basic clinical features, PCI success, and in-hospital outcomes (death, recurrent infarction, stroke, and major bleeding). Table 1 includes the main characteristics of the study population.

Statistical Analysis

Continuous variables were calculated as mean±standard deviation (SD) and categorical variables as percentages. Normally distributed continuous variables were compared with Student's t-test, non-normally distributed ones were compared with Mann-Whitney U-test. Categorical variables were compared with the Chi-square test. p value <0.05 was considered statistically significant. SPSS 16.0 program was used in Statistical analysis, (SPSS Inc., Chicago, IL).

Table 1. Main characteristics of the study population

Parameters (N=203)	**Group1** (N=42)	**Group 2** (N=161)	**P value**
Age (years ± SD)	82 ± 5	78 ± 7	0.001
Sex (male), n (%)	23 (11)	85 (42)	0.8
Gensini score	70 ± 30	42 ± 26	0.001
Hypercholesterolaemia, n (%)	12 (6)	77 (38)	0.03
Smoking, n (%)	7 (3)	11 (5)	0.06
HT, n (%)	21 (10)	92 (45)	0.5
Diabetes mellitus, n (%)	11 (5)	43 (21)	0.2
Alanin aminotransferaz (ALT)	31±25	25±18	0.8
Hgb (g/dL)	12.7±2.2	13.1±1.5	0.9
Glucose (mg/dL)	112±46	115±38	0.2
Total Cholesterol (mg/dL)	166±38	177±42	0.25
LDL (mg/dL)	103±32	113±36	0.25
HDL (mg/dL)	34 ± 7	41 ± 9	0.001
Triglyceride (mg/dL)	126±45	112±52	0.3
Creatinine clearance	46 ± 17	65 ± 18	0.001
TIMI flow			0.001
TIMI 0	13 (6)	10 (5)	
TIMI 1	10 (5)	6 (3)	
TIMI 2	6 (3)	16 (8)	
TIMI 3	13 (6)	161 (79)	
Myocardial infarction (MI)			0.01
Anteroseptal MI	27(13)	69 (64)	
Inferior MI	15(7)	92 (45)	

Table 2. The correlations of parameters with hospital mortality.

Parameters	Gensini score	Age	HDL	Creatinine clearance	Hospital mortality
Gensini score	-	r=0.246 p=0.001	r=-0.179 p=0.01	r=-0.263 p=0.001	r:0.439 p:0.001
Age	r=0.246 p=0.001	-	r=0.119 p=0.09	r=-0.452 p=0.001	r:0.273 p:0.001
HDL	r=-0.179 p=0.01	r=0.119 p=0.09	-	r=0.128 p=0.07	r:-0.282 p:0.001
Creatinine clearance	r=-0.263 p=0.001	r=-0.452 p=0.001	r=0.128 p=0.07	-	r:-0.413 p:0.001
Hospital mortality	r:0.439 p:0.001	r:0.273 p:0.001	r:-0.282 p:0.001	r:-0.413 p:0.001	-

RESULTS

In group 1, patients who died after MI, renal function (CrCl) was worse, the severity of coronary artery disease (Gensini score) and age were higher according to group 2 (age: 82 ± 5 yr, 78 ± 7 yr, p<0.001; Gensini score: 70 ± 30, 42 ± 26, p: 0.001; CrCl: 46 ± 17 mg/min, 65 ± 18 mg/min, p<0.001). HDL levels were lower in group 1 and were statistically significant. (HDL: 34 ± 7 mg/dL, 41 ± 9 mg/dL, p <0.001). Other basal characters were similar in both groups.

Explanations of abbreviations

(TIMI: Thrombolysis in myocardial infarction, HT: Hypertension,

HDL: High density lipoprotein cholesterol,

LDL: Low density lipoprotein cholesterol,

Hgb: Hemoglobin,

Gensini score: Gensini score was used to evaluate the severity of atherosclerosis. The most severe stenosis in each of the 8 coronary segments was graded from 1 to 4 (1%-49% lumen diameter reduction: 1 point; 50%-74% stenosis, 2 points; 75%-99% stenosis, 3 points; and 100% occlusion 4 points) to give a total score).

Hospital mortality correlated positively with Gensini score and advanced age, while negatively correlated with HDL and creatinine clearance (Table 2). Age: r:0.273, p:0.001; Gensini score: r:0.439, p:0.001; creatinine clearance r:-0.413, p:0.001; HDL: r:-0.282, p<0.001.

Hospital mortality correlated positively with Gensini score and advanced age, while negatively correlated with HDL and creatinine clearance. There were positive correlations between in-hospital mortality with age and coronary artery disease prevalence, and negative correlations between in-hospital mortality with CrCl and HDL (age: r: 0.273, p: 0.001; Gensini skoru: r: 0.439, p: 0.001; CrCl: r: -0.413, p: 0.001; HDL: r: -0.282, p: 0.001). Table 3 shows the results of multivariate analysis with logistic regression in hospital mortality. As a result of logistic regression multivariate analysis used to determine in-hospital mortality, crcl, HDL level and Gensini score were independent predictors of in-hospital mortality (CrCl: OR 1.057 (1.029-1.086), p = 0.001; HDL: OR 1.077 (1.021-1.136), p = 0.007; Gensini score: OR 0.969 (0.952-0.985), p = 0.001).

Table 3. Results of multivariate analysis with logistic regression for hospital mortality.

Independent Variables	P value	Odds Ratio (95% confidence interval)
Gensini score	0.001	0.969 (0.952-0.985)
HDL	0.007	1.077 (1.021-1.136)
Age (year)	0.14	0.933 (0.852-1.023)
Creatinine clearance	0.001	1.057 (1.029-1.086)
Constant	0.455	17.976
R^2 (*Cox & Snell/ Nagelkerke*)		0.3 / 0.469

In univariate analysis, determinants with a p value <0.05 were taken into the logistic regression analysis by the input method. When we performed multiple logistic regression analysis, hospital mortality was associated to group 1 creatinine clearance (CCL), (OR 1.057 (1.029-1.086), p = 0.001), HDL, (OR 1.077 (1.021-1.136), p = 0.007), Gensini score, (OR 0.969 (0.952-0.985), p = 0.001); and it was independent from group 2 creatinine clearance, HDL and Gensini score (Table 3).

DISCUSSION

In our study, it was revealed that renal dysfunction is an important risk factor increasing in-hospital mortality in geriatric patients with ST-elevation MI and primary PCI. In geriatric patients with atherosclerosis, MI, acute coronary syndrome, renal failure increases mortality and morbidity and is closely related, and there are similar studies. Clinicians' fear of elderly patients is due to their high complication rates and more fragility.[12] The prevalence of CKD increases in correlation with age. So; While it is 4% at the age of 20-39, it increases to 47% after the age of 70. [13] CKD is also an important risk factor for diseases such as heart failure and ventricular arrhythmias, which are important in the morbidity and mortality of cardiovascular diseases.[14,15] We found a significant increase in mortality, especially in elderly patients with renal failure who had MI. Current guidelines recommend intervention and treatment in patients with STEMI and renal dysfunction in the same way as other STEMI patients, taking into account some precautions during the administration of contrast dye and some drugs.[16] Aging causes both structural and functional changes in the kidneys. Reduction of renal blood flow and a number of nephrons with aging cause CKD by decreasing glomerular filtration rate.

Chronic kidney disease (CKD) is set in 5 stages of increasing severity with a decrease in glomerular filtration rate leading to end stage renal disease (ESRD) requiring a treatment of substitution, dialysis or transplantation. CKD is frequent, it increases with age, and affects one person out of 10 in the general population, and only 4 per 100,000 will reach end-stage renal disease (ESRD). As soon as it occurs, CKD is associated with increased cardiovascular comorbid conditions. [17]

Chronic renal disease has a high mortality and morbidity, especially due to cardiovascular diseases. Cardiovascular risk increases exponentially as the CKD stage progresses. For example, cardiovascular risk increases 2 to 4 times in a patient in stage 3, and 10 to 50 times in a patient in stage 5.[18]

In recent studies, aggressive revascularization strategies have been shown to provide more survival and absolute risk reduction in terms of better quality of life in patients over 75 years of age than younger patients.[19-21]

The main finding of our study, coronary artery revascularization in elderly patients with low CrCl was found to be more applicable, safe and associated with better outcome than medical treatment. This was also the case in elderly patients who were susceptible to bleeding, contrast nephropathy, in-hospital bleeding, and toxic effects from treatment. Studies in this area, especially in geriatric patients, have also achieved similar results to our study. as follows: In patients with ST-segment elevation MI (STEMI) and without STEMI, patients with kidney disease have a higher mortality than patients with preserved kidney function.[22-24] Currently, primary PCI in STEMI patients is included in the recommended reperfusion strategy and also in those with renal dysfunction. Since primary PCI is an emergency treatment in STEMI patients, renal function and CrCl levels are unknown in these patients during the procedure. Records show that most patients are diagnosed outside the hospital and referred directly to the catheterization laboratory, with the first blood samples taken prior to contrast injection for biochemical testing.[25] While guidelines recommend evaluation of risk-benefit ratio with severity of renal dysfunction, an early invasive approach remains the best strategy for patients with acute coronary syndrome with CKD.26

In our study, patients with renal dysfunction who underwent primary PCI were fewer in number than

patients without renal dysfunction. In our study, as in other studies, the presence of CKD increases short-term and long-term mortality. This situation, the presence of RI, has seen a higher 30-day increase in mortality, similar to previous studies. In addition, the presence of kidney disease in STEMI and non-STEMI patients has been associated with an increase in 9-month mortality, depending on all causes.[27-30] According to our study, RI (renal insufficiency) is an independent predictor of increasing 1-year mortality.

Renal dysfunction increases mortality during hospitalization in elderly patients who underwent primary percutaneous coronary intervention and had myocardial infarction. Renal dysfunction in elderly patients with MI, like other cardiovascular risk factors, increases mortality during hospitalization. Taking these factors into account and taking precautions in geriatric patients with MI would play an important role in reducing in-hospital mortality.

CONCLUSION

Renal dysfunction increases in-hospital mortality in elderly patients with STEMI undergoing primary PCI. Renal dysfunction in elderly patients with MI is an important risk factor that increases in-hospital mortality like other cardiovascular risk factors.

Limitations

Our findings can be affected by data quality and confounding variables. In addition, our study is open to bias regarding unmeasurable factors. We tried to reduce the bias caused by these unknown variables as much as possible. St-elevation MI patients with cardiogenic shock that might be subject to the study were not excluded. Our systematic access to additional information about creatinine values or contrast-induced nephropathy was limited in the days after primary PCI was performed.

Ethics Committee Approval

Ethics Committee the ethics committee approval of the study at non-interventional clinical studies ethics committee of Recep Tayyip Erdogan University (Local Ethical Committee) (Decision no: 2016/13).

Informed Consent

Informed consent was obtained from the patients who participated in this study.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

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Olgu Sunumu
Case Report

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Ovarian Torsion in The Third Trimester of a Twin Pregnancy: A Case Report

İkiz Gebeliğin Üçüncü Trimesterinde Over Torsiyonu: Olgu Sunumu

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ABSTRACT

During pregnancy, ovarian torsion (OT) occurs at a rate of 1 to 5 per 100,000 and is extremely uncommon. There is only one case report of OT occurring in a third-trimester, twin pregnancy. In the present case, a 30-year-old female patient whose first pregnancy was dichorionic diamniotic and at 30 weeks of age was admitted to our emergency service with the complaint of chronic pain. The patient had a history of spontaneous pregnancy and an increase in carcinoembryonic antigen level was found in her biochemical indicators. Magnetic resonance imaging and Doppler ultrasound indicated OT, therefore she had surgery that involved making a midline incision under the umbilicus. Both ovary and tuba uteri were removed as they were necrotic and twist on the right side of the adnexa. No complications developed following the surgery and pathology showed mucinous cyst adenoma. The most common causes of abdominal pain in the third trimester are gas, constipation, Braxton-Hicks, urinary tract infection, appendicitis, and preeclampsia. Although OT is extremely rare in the third trimester of spontaneous twin pregnancies, it should be considered in the differential diagnosis.

Keywords: Torsion, Twin pregnancy, Third trimester

ÖZET

Hamilelik sırasında over torsiyonu (OT) 100.000'de 1 ila 5 oranında meydana gelir ve oldukça nadirdir. Üçüncü üç aylık dönemde, ikiz gebelikte meydana gelen OT ile ilgili yalnızca bir vaka raporu vardır. Bizim olgumuzda 30 yaşında, ilk gebeliği olan dikoryonik diamniyotik 30 haftalık kadın hasta, kronik ağrı şikayeti ile acil servisimize başvurdu. Spontan gebelik öyküsü olan hastanın biyokimyasal göstergelerinde karsinoembriyonik antijen düzeylerinde yükseklik saptandı. Manyetik rezonans görüntüleme ve Doppler ultrason OT lehineydi, bu nedenle göbek altında orta hat insizyonu ile ameliyat edildi. Hem yumurtalık hem de tuba uteri, nekrotik olduklarından ve adneksin sağ tarafında büküldüklerinden dolayı çıkarıldı. Ameliyat sonrası herhangi bir komplikasyon gelişmedi ve patoloji müsinöz kist adenomu olarak geldi. Üçüncü trimesterde karın ağrısının en yaygın nedenleri gaz, kabızlık, Braxton-Hicks, idrar yolu enfeksiyonu, apandisit ve preeklampsidir. Spontan ikiz gebeliklerin üçüncü trimesterinde OT oldukça nadir olmakla birlikte ayırıcı tanıda gözönünde bulundurulmalıdır.

Anahtar Kelimeler: Torsiyon, İkiz gebelik, Üçüncü trimester

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INTRODUCTION

Ovarian torsion (OT) is the rotation of the pedicle, which contains the arterial and venous vessels of the ovary, on its axis in a partial or full turn, preventing blood flow. OT can damage women of any age, and early surgical treatment has the potential to preserve ovarian and tubal functions.[1] OT is rarely reported in the third trimester in singleton pregnancies. There was only one case in which they reported OT in spontaneous twin pregnancy in the third trimester.[2]

CASE REPORT

A 30-year-old dichorionic diamniotic pregnant woman who had her first pregnancy was admitted to our hospital with persistent pain in the right upper quadrant. After evaluation in another obstetrics clinic, the pregnant case was referred to our hospital, which is a tertiary hospital, to investigate other urological and surgical causes. The patient had no complaints of nausea or vomiting, and her vital signs were normal. There was tenderness in the right upper quadrant, but no signs of defense were seen on the abdominal examination. The patient had no history of previous abdominal surgery. In the non-contrast abdominal MRI examination of the patient, no finding in favor of appendicitis and renal stones were detected. The value of the carcinoembryonic antigen was 16 ng/mL. Furthermore, other blood and urine tests showed normal results (Table 1). A 5-centimeter cyst was detected in the patient's right ovary two years ago. A mass with features compatible with an ovarian cyst was detected in the right upper quadrant (Fig. 1).Ultrasonography (USG) showed viable, dichorionic diamniotic twin pregnancy compatible with 30 weeks gestation. A septal cyst of 80.6 x 73.3 mm was detected in the ovary in the right upper quadrant (Fig. 2). No blood flow was detected in the ovarian Doppler ultrasound examination. No contraction was detected in cardiotocography. Cervical length was safe on ultrasound. The patient with acute abdominal pain and suspected right OT was operated with a midline incision under the umbilicus. Tocolysis was not applied before and during the operation. Torsion occurred in the adnexa on the right. The right ovary was found to have a mass of around 8 centimeters in diameter. It had rotated around itself for about 4 turns. Right salpingo-opherectomy was performed because of the appearance of necrosis and tumor suspicion (Fig. 3 & Fig. 4). The operation time lasted 20 minutes in the patient who underwent spinal anesthesia. During the postoperative follow-up, we did not find any signs of complications. During the pathological investigation, the presence of a mucinous cyst adenoma was found.

DISCUSSION

OT is encountered at a rate of 1 to 5 per hundred thousand during pregnancy and is very rare.[3] Smits et al reported the rate of spontaneous twin birth as 0.6% to 2.79%, and the rate of twin birth among those who underwent assisted reproductive technology was 6.8% to 8.44%.[4] In the literature, OT has been reported in the third trimester in a twin pregnancy obtained by assisted reproductive techniques.[5] In the present case, ovarian torsion was observed in a spontaneous twin pregnancy case. Most of the patients with ovarian torsion (80%) have an ovarian mass larger than 5 cm and it is the most important risk factor.[1] In the current case, the patient had a history of ovarian cysts. Therefore, it is likely that this may have been the main risk factor in the development of ovarian torsion. OT gives similar clinical findings to non-pregnant women in pregnant women.[6] The most common clinical findings are pelvic pain, ovarian mass, nausea, vomiting, and fever.[7] Nausea, vomiting, and fever were not observed in the present case, and severe abdominal pain and pelvic mass were detected. USG and MRI are the imaging methods used in differentiating the main causes of acute abdomen (appendicitis, ovarian cyst rupture, and degenerated myoma).[8] A high sensitivity (76-100%) and specificity (94-100%) can be achieved with abnormal Doppler USG in the diagnosis of OT.[9] In the present case, ovarian blood flow was not observed in the patient. Management is like non-pregnant women, but it may not be easy to operate laparoscopically when a pregnant uterus is considered.[10] In the present case, laparotomy was preferred because it was in the third trimester of pregnancy and because it was a twin pregnancy. In the third trimester of a patient who was pregnant with twins, a midline surgical incision was made under the umbilicus because the position of the ovary could shift. The midline incision was necessary to provide the surgeon with a clear view of the operative field, allowing them to identify and protect any nearby organs that might be at risk during the surgery. OT has been reported in the current literature in a third trimester pregnant woman with spontaneous twin pregnancy.[2] In the described case, no mass was observed in the ovary, only detorsion was applied. After the detorsion was

applied, the patient was monitored closely and discharged with a follow-up plan.

Table 1. Analysis of blood and urine samples at the time of admission to the hospital

	Result	The reference range
Leukocyte (K/uL)	10.7	3.7 - 10.1
Hemoglobin (g/dL)	10.4	12 - 17
Hematocrit (%)	30.9	37 - 54
Platelet (K/uL)	178	100 - 400
C reactive protein (mg/L)	8.31	0 - 5
Creatine (mg/dL)	0.39	0.57 - 1.11
Total bilirubin (mg/dL)	0.37	0.2 - 1.2
Direct bilirubin (mg/dL)	0.14	0 - 0.5
Carcinoembryonic antigen (ng/ml)	16	0 - 2.5
Urine protein	negative	
Urine ketone	1+	
Urine nitrit	negative	
Urine leukocyte	negative	
Urine erythrocyte	negative	

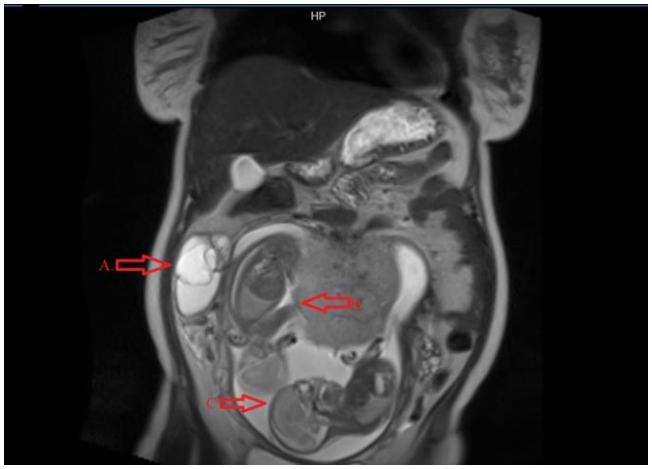

Figure 1. In non-contrast MR examination, A. Right ovarian mass, B. Upper fetus, C. Lower fetus

CONCLUSION

The most common causes of abdominal pain in the third trimester are gas, constipation, Braxton-Hicks, urinary tract infection, appendicitis, and preeclampsia. OT in the third trimester of a twin pregnancy is uncommon, but it should be considered in the differential diagnosis. Despite the relative rarity, it is important to be aware of this possibility.

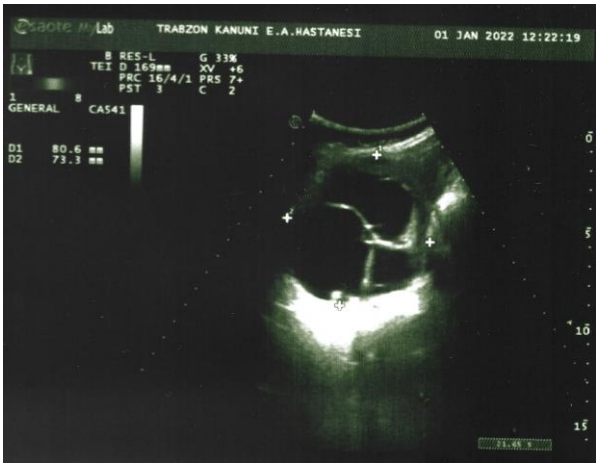

Figure 2. Septal cyst in the right ovary on ultrasound examination

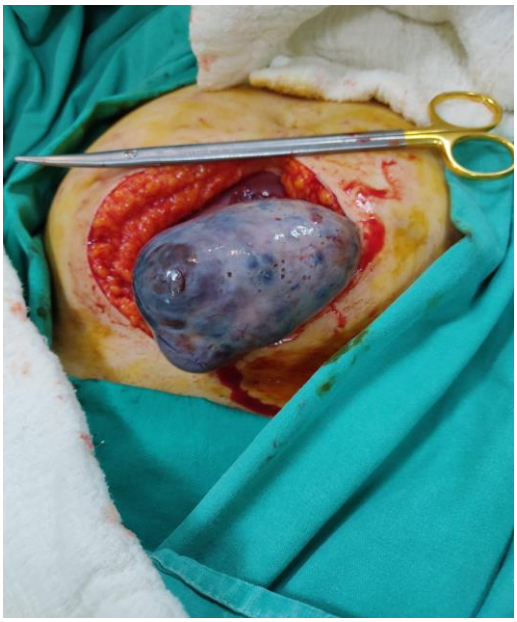

Figure 3. Necrosis of the right adnex

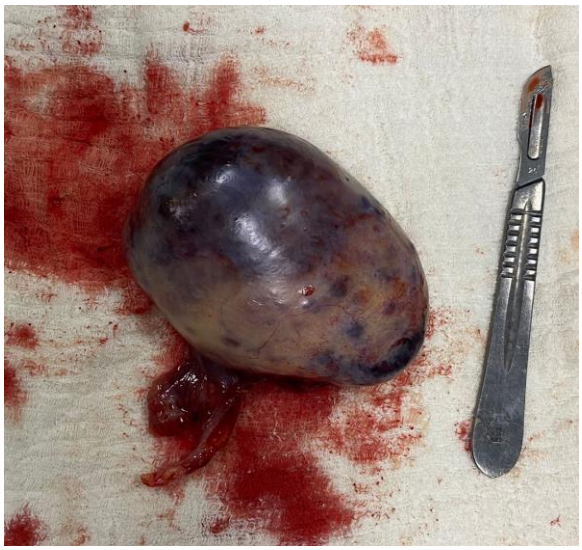

Figure 4. Right ovary and tuba uterina

Authorship contribution statement

Consept and desing: D.K., E.A.R.

Acquisition of data: D.K., E.A.R.

Analysis and interpretation of data: D.K., K.E

Drafting of the manuscript: D.K., K.E., R.E.

Critical revision of the manuscript for important intellectual content: R.E., Y.B.T.

Supervision: Y.B.T.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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SCUBE1 and Irisin Relation in Bladder Cancer

Mesane Kanserinde SCUBE1 ve İrisin İlişkisi

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ABSTRACT

Bladder Cancer (BC) is a urogenital system disease with a frequency of approximately 11.000 new cases. The major risk factors of BC are smoking and exposure to industrial carcinogens. The diagnosis and monitoring of BC largely consist of invasive tests involving periodic cystoscopy. This method is known as the gold standard although this is a trustworthy method the procedure is highly disturbing for the cancer patient and causes comorbidity. That's why; non-invasive diagnostic methods continue to be researched. Signal Peptide CUB Epidermal Growth Factor 1 Containing Protein (SCUBE1) is a member of the SCUBE family. SCUBE1 is often closely associated with pathological conditions such as thrombus, atherosclerotic plaque, inflammation, and hypoxia-related disorders. Many recent studies have focused on the expression and function of the SCUBE family in cancer. Studies of the SCUBE family have demonstrated the potential to develop as a diagnostic or prognostic biomarker in cancer. Irisin is an adipocytokine produced by proteolytic cleavage of the fibronectin type III domain-containing protein 5 (FNDC5). There are many studies examining the relationship between irisin and cancer. Although SCUBE1 and irisin have been evaluated as early diagnosis biomarkers of bladder cancer in many studies, no study evaluating the parameters together has been found. In the future, multicenter studies evaluating SCUBE1 and irisin parameters together are needed for the early diagnosis of bladder cancer in people who smoke and are exposed to various chemicals.

Keywords: Bladder cancer, Irisin, SCUBE1

ÖZET

Mesane Kanseri (MK) yaklaşık 11,000 yeni vaka sıklığına sahip ürogenital sistem hastalığıdır. Mesane kanserinin başlıca risk faktörleri sigara içmek ve endüstriyel kanserojenlere maruz kalmaktır. MK'nın teşhisi ve izlenmesi büyük ölçüde periyodik sistoskopiyi içeren invaziv testlerden oluşur. Bu yöntem altın standart olarak bilinir, güvenilir bir yöntem olmasına rağmen işlem hasta için oldukça rahatsız edicidir ve komorbiditeye neden olur. Bu nedenle non-invaziv tanı yöntemleri araştırılmaya devam etmektedir. Sinyal Peptit CUB Epidermal Büyüme Faktörü 1 İçeren Protein (SCUBE1), SCUBE ailesinin bir üyesidir. SCUBE1 genellikle trombüs, aterosklerotik plak, inflamasyon ve hipoksi ile ilişkili bozukluklar gibi patolojik durumlarla yakından ilişkilidir. Son zamanlarda yapılan birçok çalışma da SCUBE ailesinin kanserdeki ekspresyonu ve işlevine odaklanılmaktadır. SCUBE ailesi ile ilgili yapılan çalışmalar, kanserde teşhis veya prognostik bir biyobelirteç olarak gelişme potansiyeli olduğunu göstermiştir. İrisin, Fibronektin Tip III Domainini İçeren 5. proteinin (FNDC5) proteolitik bölünmesiyle üretilen bir adipomiyokindir. İrisin ve kanser arasındaki ilişkiyi inceleyen birçok araştırma vardır. SCUBE1 ve irisin, birçok çalışmada mesane kanseri için erken tanı biyobelirteci olarak değerlendirilmesine rağmen parametreleri birlikte değerlendiren bir çalışmaya rastlanılmamıştır. Gelecekte, sigara içen ve çeşitli kimyasalara maruz kalan kişilerde erken mesane kanseri tanısı için SCUBE1 ve irisin parametrelerini birlikte değerlendiren çok merkezli çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Mesane kanseri, İrisin, SCUBE1

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INTRODUCTION

Bladder cancer (BC, BCa) is the second most frequently seen urogenital cancer, involving approximately 350,000 new cases and 150,000 deaths worldwide each year. It is also a major cause of morbidity and mortality. The tumor may sometimes not directly infiltrate the bladder muscle, but due to its high histological grade, this may herald a transition to infiltration of that muscle.[1] First evaluated in the 1950s, tobacco smoking is the most important risk factor for BC development in both men and women and, because of its high prevalence, is responsible for the majority of BC cases.[2] It contains several compounds such as aromatic amines, polycyclic aromatic hydrocarbons, heterocyclic amines, and N-nitroso compounds leading to a DNA damage via single-strand and double-strand DNA breaks, and base modifications. Moreover, the reactive oxygen species present in high concentrations in tobacco smoke, directly induce DNA damage and accumulate in bladder epithelium as result of the metabolism of chemical carcinogens.[3] Bladder cancer is nearly three times more common in smokers than nonsmokers.[4] In addition to bladder cancer, tobacco smoking is strongly associated with increased risk of lung cancer.[5] Chemicals in tobacco increase the expression of proteins involved in inflammation, and activate genetic and epigenetic pathways, thereby adversely affecting the cell cycle through the induction of uncontrolled cell proliferation.[6] BC is a highly complex entity involving various molecular and pathological pathways. Its behavior therefore varies in line with the clinical stage of the tumor and its molecular type. The diagnosis and follow-up of BC largely involve invasive tests involving periodic cystoscopy, a method regarded as the gold standard.[7] Despite being trustworthy, this procedure is distinctly unpleasant for the patient and causes comorbidity. Research into non-invasive diagnostic methods is continuing. In a previous study estimating potential biomarkers in bladder cancer, Sakinewicz et al. reported that podoplanin exhibited 72% sensitivity and 69% selectivity.[8] Tokarzewicz et al. demonstrated that cystatin C exhibited 87% sensitivity and 92% specificity in patients with BC.[9] Wang et al. also reported that bladder cancer-specific antigen-1 exhibits 74% sensitivity and 69% specificity.[10] Interestingly, Guszcz et al. showed that the plasma aromatase biomarker exhibited 100% sensitivity and 100% specificity in their recent study of 78 patients with BC and 18 healthy controls.[11]

Signal Peptide-Cub-Epidermal Growth Factor Domain-Containing Protein 1 (SCUBE1)

SCUBE1 is one of the members of the SCUBE family and a branch of the epidermal growth factor (EGF) superfamily. This has been shown to occur in various domain structures, such as cysteine-rich and EGF-like repeats, and the CUB domain. The SCUBE family consists of three distinct members: SCUBE1, SCUBE2, and SCUBE3.[12] SCUBE1 is a cell surface glycoprotein expressed and released during early embryogenesis and present in both platelet and endothelial cells. SCUBE1 is stored inside alpha granules in inactive platelets. Following activation by thrombin, it shifts to the platelet surface and enters the thrombus through secretion in small-sized soluble particles. Platelets are known to play a significant role between inflammation and thrombosis, and vascular and tissue repair mechanisms. The association between thrombosis and cancer was first set out by Trousseau. Trousseau's syndrome cancer-associated thrombosis) is the second leading cause of mortality in cancer patients after death resulting from cancer itself.[13] The risk of venous thromboembolism is 4-7 times greater in patients with cancer than cancer free individuals.[14] SCUBE1 may indicate hypercoagulability in patients with breast cancer and thus be useful in terms of identifying individuals with a greater risk of thrombosis and requiring anti-thrombotic therapy. SCUBE1 can also be employed as an adjunct test for identifying individuals with a potential risk of breast cancer.[12] A previous study reported significantly higher SCUBE 1 titers in patients with gastric cancer than those in a control group.[15] Karaguzel et al. concluded that SCUBE1 may constitute a promising biomarker in the diagnosis and follow-up of renal tumors.[16] A very recent study by Mentese et al. demonstrated that the sensitivity and specificity of SCUBE1 appear to be quite similar to those of CAIX , an AUC value of 0.879 for SCUBE1 was associated with 71% sensitivity and 92% specificity, while an AUC value of 0.891 for CAIX was associated with 93% sensitivity and 78% specificity. Those authors suggested that increased SCUBE1 levels may be a useful addition to clinical findings of disease in the diagnosis of BC.[7] For the first time in the literature, serum SCUBE1 values in BC patients were found to be statistically higher than in the healthy control group in Mentese and his friends study. The majority of studies to date have concentrated on the expression of the SCUBE family and

its functions in the context of cancer. However, further research into the family's role in other tumors is still needed. Conditional engineered mouse models may yield useful findings concerning the function of SCUBE and the mechanisms involved in its role in cancer progression. There is a need for systematic approaches to screening SCUBE family protein substrates and interactions with other proteins that may yield information regarding their physiological role and mapping in various forms of cancer. Previous research into the SCUBE family has indicated the potential for use as a diagnostic and/or prognostic biomarker in cancer.[17]

Irisin

Irisin is an adipocytokine produced by the proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5). Various recent studies have investigated the relationship between irisin and cancer.[18] Irisin has been shown to activate the adenosine monophosphate-activated protein kinase (AMPK) pathway and to inhibit the mammalian target of rapamycin (mTOR) signaling. Studies have also reported that irisin inhibits pancreatic cancer cell growth via the activation of AMPK, thus downregulating the has occurred in the rate of BC. Early diagnosis is therefore particularly important. SCUBE1 and irisin have been investigated by various researchers as early diagnostic biomarkers in BC, but our search of the literature revealed no studies evaluating these two parameters together.[3,25,26] The ELISA kits used in these studies were designed for research purposes and their diagnostic effectiveness has not been fully confirmed. The sensitivity and specificity of ELISA kits produced by different manufacturers may vary, and differences in absolute values are possible. Similar problems apply to different biochemical parameters. This can be resolved by the development ELISA kits exhibiting high sensitivity and specificity for serum irisin measurement, or through the discovery of high-sensitivity methods capable of measuring irisin levels by high pressure liquid chromatography (HPLC) or LC-MS/MS (Tandem MS). mTOR pathway and suppressing the epithelial-mesenchymal transition (EMT) of pancreatic cancer cells.[19] Moon et al. reported that physiological (5-10 nmol/L) and physiologically/pharmacologically elevated irisin concentrations (50-100 nmol/L) exhibited no effect on cell proliferation or the malignancy potential of obesity-related cancer cell lines in vitro.[20] Us Altay et al. reported that circulating irisin levels increased with the development of GC.[21] Other research reporting increased irisin immunoreactivity in breast, ovary, and cervix carcinoma tissues, and in endometrial hyperplasia suggested that this peptide may be of critical importance during carcinogenesis.[22] Provatopoulou et al. investigated the relationship between irisin and breast cancer and reported significantly lower serum irisin levels in patients with breast cancer than in healthy controls.[23] Aydın et al. employed irisin antibody immunohistochemistry to examine alterations in irisin expression in gastrointestinal cancers compared to healthy tissues. Histoscores (area intensity values) revealed significant increases in irisin levels in gastrointestinal cancer tissues, although not in hepatic cancers.[24] Gaggini et al. reported increased FNDC5/irisin expression in human hepatocellular carcinoma increased.[25] Shoa et al. demonstrated that irisin inhibits lung cell migration, proliferation, and invasion by suppressing epithelial-to-mesenchymal transition.[26] In vivo studies also indicate that irisin may represent an excellent diagnostic factor for cancer.[27,28] Esawy and Abdel-Samd revealed significantly lower levels of serum irisin in patients with BC and postulated that serum irisin concentrations may represent an excellent diagnostic and prognostic marker for BC.[29] Taken et al. also demonstrated that serum irisin levels are capable of employment in the diagnosis of BC. Irisin concentrations can also be of assistance in differentiating high-grade stage tumors.[30] Despite the apparent similarities between Esawy and Taken's studies, there are also some differences. Other malignancies were excluded in Esawy's study, although obesity and other chronic diseases were included, while Taken's study excluded all these diseases. As described above, one particular difficulty with BC is that it cannot be diagnosed early using non-invasive methods.

CONCLUSION AND RECOMMENDATIONS

Evidence demonstrates that the diagnosis of BC, the ninth most common type of cancer worldwide, occurs at a much older age than any other type of cancer. The number of BC cases may be expected to rise in line with life expectancy. The diagnosis and monitoring of BC largely involve invasive tests involving periodic cystoscopy, regarded as the gold standard. Although this is a reliable method, the procedure is a particular source of discomfort for the patient and causes comorbidity.

Table 1. Sensitivity and Specificity of potential biomarkers of BC.

BC biomarkers	Sensitivity	Specificity
SCUBE1[7]	71%	92%
CAIX[7]	93%	78%
Plasma Aromatase Biomarker[11]	100%	100%
Podoplanin[8]	72%	69%
Cystatin C[9]	87%	92%
Bladder cancer-specific antigen-1[10]	74%	69%

Research into non-invasive diagnostic methods is therefore still taking place.

Highlights for future research:

• Evaluation of SCUBE1 and irisin parameters in combination in smoker and non-smoker bladder cancer patients,

• The use of ELISA kits with higher sensitivity and specificity,

• The principal limitation of previous studies is the low number of cancer patients and control cases, and multicenter studies with larger patient series are now needed.

Authorship contribution statement

(Single author) DUA contributed to the conceptualization, data collection, and writing manuscript.

Declaration of competing interest

The author has no potential conflicts of interest to disclose.

Availability of data and materials

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Omuz Cerrahilerinde Anestezi ve Postoperatif Analjezi Yöntemleri

Anesthesia and Postoperative Analgesia Methods in Shoulder Surgeries

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ÖZET

Omuz cerrahisi ve onunla ilgili anestezi ve analjezi yöntemlerine olan ilgi giderek artmaktadır. Omuz dik vücut pozisyonu ve özellikle bayanlarda estetik görünüm için çok önemlidir. Omuz eklemi insan vücudundaki bütün eklemler içinde en geniş hareket aralığına sahip olan eklemdir. Bütün omuz prosedürleri hem hasta konforu hem de rehabilitasyon egzersizlerinin erkenden yapılabilmesi için yeterli anestezi ve analjeziye gereksinim duymaktadır. Güncel klinik pratikte genel anestezi veya infiltrasyon gibi sinir blokları ve interskalen blok gibi üst ekstremite blokları omuz cerrahilerinde başarıyla kullanılmaktadır. Anestezi ve analjezi tekniklerini omuz cerrahisinde karşılaştırdığımızda tekniğin ağrı kontrolünde etkinliğini, yan etki insidansını ve hasta memnuniyetini göz önüne almalıyız.

Anahtar Kelimeler: Anestezi, Postoperatif analjezi, Omuz cerrahisi

ABSTRACT

There is an increasing interest in shoulder surgery and related anesthesia and analgesia methods. The shoulder is very important for a vertical body position and cosmetic appearance particularly in women. The shoulder joint has the largest motion range of all joints in the human body. All of the shoulder procedures need adequate anesthesia and analgesia for both the comfort of the patients and an early use of rehabilitation exercise. In current clinical practice general anesthesia or nerve blocks like infiltration and interscalene block like upper extremity blocks can be used for shoulder surgeries. When compared the anesthesia and analgesia techniques for shoulder surgery we should consider the effectiveness of pain control, incidence of side effects, and patient satisfaction of the techniques.

Keywords: Anesthesia, Postoperative analgesia, Shoulder surgery

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GİRİŞ

Omuz ve omuz eklemi insan vücudunun çok önemli kısımlarındandır. Omuz, vücudun vertikal pozisyonu için önemli olmakla birlikte özellikle bayanlarda kozmetik görünüm için de dikkat çekmektedir. Omuz eklemi ise insan vücudundaki tüm eklemler arasında en geniş hareket aralığına sahip eklemdir.[1] Omuz cerrahisi prosedürleri aşağıdaki gibi sıralanabilir: tanısal artroskopi, subakromiyal bozukluklar (impingement-sıkışma- sendromu, rotator manşet defektleri ve yırtıkları (yüzeysel, eklemsel, tam kalınlıkta), periartritis humeroscapularis, tendinopati), atroskopik subakromiyal dekompresyon (Tablo 1). Bütün bu omuz prosedürleri anestezi ve analjeziye gereksinim duymaktadır. Omuz cerrahisi işlemlerinden sonra ağrının yeterince dindirilmesi hem hastanın konforu hem de ameliyat sonrası gerekli rehabilitasyon egzersizlerin erken dönemde ve düzenli olarak yapılabilmesi için gereklidir.[2] Bu derlemenin amacı omuz cerrahisi işlemlerinde anestezi ve analjezi yöntemlerini tartışmak ve bu alanda bazı öneriler sunmaktır.

Omuz cerrahilerinde kullanılan güncel anestezi ve analjezi teknikleri

Günlük pratikte omuz cerrahisi işlemlerinde genel anestezi, rejyonal anestezi ve sinir blokları kullanılmaktadır. Bu anestezi tekniklerinin omuz cerrahisinde perioperatif sonuçları tartışmalıdır. Rejyonal anestezi teknikleri genel anestezi ile karşılaştırıldığında bazı cerrahi işlemlerde önemli avantajlar sağlamaktadır. Rejyonal anestezi sadece yeterli cerrahi anestezi için yapılmaz aynı zamanda mükemmel ağrı kontrolü, daha az yan etki, kan kaybının azaltılması, pulmoner ve kardiyak fonksiyonların korunması ve daha çabuk derlenmenin sağlanması gibi avantajları da vardır.[3-7] Bununla birlikte rejyonal anestezi teknikleri Horner sendromu, geçici işitme kaybı, sistemik lokal anestezik toksisitesi, ipsilateral diyafragmatik parezi, frenik sinir palsi ve diğer sinir hasarlarına yol açabilmektedir.[8-10]

Periferik ve santral blokların yapılması sırasında günümüzde ultrason kullanılmasının klinik pratiğe büyük katkıları olmuştur. Bloklar yapılırken gerçek zamanlı ultrason kullanımı işlem süresini kısaltmış, başarı oranını artırmış, komplikasyonları azaltmış ve kullanılan toplam ilaç dozlarını düşürmüştür. Ayrıca yaşlılar, eşlik eden başka sorunları olanlar ve ağır sistemik problemi olan hastalarda güvenli anestezi uygulama imkanı doğurmuştur.[11] Ultrason rehberliğinde interskalen blok yapılan bir çalışmada kullanılan lokal anestezik dozunun azaldığı ve dolaysıyla lokal anestezik sistemik toksisite insidansının da azaldığı bununla birlikte olası frenik sinir felcinin de azaldığı görülmüştür.[12]

Omuz cerrahisi sonrası ağrının dindirilmesi

Omuz cerrahisi sonrası post operatif ağrının dindirilmesi için pek çok yöntem kullanılmaktadır. Bunları analjeziklerin lokal olarak subakromial bursaya injeksiyonu[13,14], intravenöz hasta kontrollü analjezi (iv PCA)[15], hasta kontrollü interskalen analjezi[6,16], analjeziklerin sürekli olarak intrabursal infüzyou[2,17], kostoklavikular blok, proksimal suprascapular sinir bloğu ve supraclavikular sinir bloğu[18] olarak sıralayabiliriz. Hasta kontrollü subakromial analjezinin omuz cerrahisi sonrası etkisini araştıran çalışmalar sınırlıdır. Bir randomize prospektif klinik çalışmada açık akromioplasti sonrası ilk olarak ropivakain veya fentanil ile yapılan hasta kontrollü subakromial analjezi fentanil ile yapılan intravenöz hasta kontrollü analjezi ile karşılaştırılmıştır. Bu çalışmada subakromial hasta kontrollü tekniklerde %0.2 ropivakain ve 4mg/mL fentanil 5 mL/saat hızında, bolus doz 3 mL, kilitli kalma süresi 20 dakika olarak uygulanmış ve benzer tarzda yeterli ağrı kontrolü minimal yan etki ve yüksek hasta memnuniyetiyle birlikte sağlanmıştır. Oysa, hasta kontrollü subakromial fentanil grubunda subakromial ropivakain veya intravenöz fentanil kadar etkin bir ağrı kontrolü sağlanamadığı bildirilmiştir.[2] Bununla birlikte, bir retrospektif klinik çalışmada interskalen blok (ISB) alan hastalar subakromial infüzyon (SAI) alan hastalardan anlamlı derecede daha az ağrı deneyimlemişlerdir ve bu ISB olan hastalar SAI alan hastalardan daha kısa sürede, onların yarısı kadar bir sürede hastaneden taburcu edilmişlerdir. Gözlemlenen bu sonuç üzerine çalışmanın yazarları SAI'nın ISB yerini günü birlik artroskopik rotator kaf onarımı sonrası alamayacağını bildirdiler.[19]

Bir üst ekstremite sinir bloğu olan interskalen blok omuz cerrahisinde hem anestezi hem de analjezi sağlamak için kullanılır. Bir prospektif, randomize, kontrollü çalışmada aynı volüm ve konsantrasyonda (30 mL ve %0.5) bupivakain ve ropivakain omuz cerrahisinde benzer cerrahi anestezi oluşturduğu bildirildi. Bu blok bir katater vasıtasıyla hasta kontrollü interskalen infüzyonla postoperatif ağrı kontrolü için sürdürüldüğünde %0.15 bupivakain ve ropivakainin yeterli analjezi sağladığı, benzer yan etkilere yol açtığı ve yüksek hasta memnuniyeti oluşturduğu

kaydedilmiştir.[16] Interskalen blok, genel anestezi ve intravenöz analjezi günübirlik omuz prosedürlerinde karşılaştırılmış ve klinik sonuçların üç grup arasında karşılaştırılabilir olduğu bildirilmiş, ancak en kısa total işlem süresinin ve en yüksek hasta memnuniyetinin interskalen grubundaki hastalarda bulunduğu bildirilmiştir.[20] Bir diğer retrospektif çalışmada ise artroskopik rotator kaf tamiri sırasında sürekli interskalen infüzyonun sürekli ağrı kontrolü sağlayabildiği ancak geçici parmak paralizisi ve ilaç kaçağı gibi komplikasyonlara da yol açabileceği bildirildi.[21] Ayrıca ISB geçici veya uzun süreli solunumsal komplikasyonlarla ilişkili olabileceği düşünülmektedir. Bunlar frenik sinir paralizisi ve tek taraflı diyafragma paralizisi olarak öne çıkmaktadır. ISB sonrası uzun süreli frenik sinir paralizisi son zamanlarda geniş bir yer bulmaktadır. Bir komplikasyon olarak ISB sonrası uzun süreli frenik sinir paralizisinin potansiyel sebepleri arasında direk iğne travması veya intranöral enjeksiyon bazı olgu sunumlarında bildirilmeydi. Ancak ultrason kılavuzluğunda ISB yapılmasıyla bu komplikasyon artık bildirilmemektedir. Kombine suprakapsuler ve aksiller sinir bloklarının yapılması frenik sinir palsisinden kaçınmak için özellikle artroskopik omuz cerrahilerinde diğer bir alternatiftir.[22] Bir derleme makalede suprakapsuler blok ile ISB arasında klinik olarak anlamlı analjezik fark olmadığı ancak derlenme odasında ISB'un daha iyi ağrı kontrolü sağladığı bildirilmiştir. Bununla birlikte suprakapsuler bloğun daha az yan etkiye yol açtığı ve bu durumun ISB kullanımını obez, uyku apnesi veya pulmoner hastalığı olan kişilerde sınırlandırabileceğini bildirmiştir. Buradan hareketle suprakapsuler bloğun omuz cerrahisinde ISB için bir alternatif olabileceği kaydedilmiştir.[8] Bazı yazarlar pulmoner komplikasyonları en aza indirmek için diyafram koruyucu rejyonal bloklar düzenlediler. Bunlar kostoklaviküler blok, proksimal suprakapsuler sinir bloğu (SSNB), suprakapsuler sinir bloğu (SCNB); ayrıca ilaveten kostoklaviküler blok kombine proksimal SSNB ile veya kostoklaviküler blok kombine SCNB ile olarak sıralanabilir. Bu yazarlar pulmoner fonksiyonu azalmış hastalarda omuz cerrahisi anestezisi için kostoklaviküler blok kombine proksimal SSNB veya SCNB önermişlerdir.[18] Bütün bunlara rağmen bir sistemik derleme ve meta analiz artroskopik rotator manşet onarımı sonrası lipozomal bupivakain ile yapılan interskalen bloğun ilk 48 saatte ağrı dindirmede, opioid kullanmada ve yan etki bakımından mükemmel olduğunu bildirmiştir.[23]

Omuz cerrahisi geçiren hastalarda brakial pleksusun tek atış interskalen bloğu (SSIB) ameliyat sonrası sekiz saate kadar analjezi sağladığı ve opioid tüketiminin azaltılması, postoperatif bulantı ve kusma görülme oranının düşmesi gibi bazı yararlı etkileri olduğu bir sistemik derleme ve meta analiz çalışmasında bildirilmiştir.[24] Bojaxhi ve arkadaşları[25] yeni bir çalışmada SSIB ve periartiküler lokal infiltrasyon analjezisi (LIA) uygulamasının sonuçlarını omuz artroplasti hastalarında açıkladılar. Bu çalışmada, sürekli interskalen blok (CISB) ile SSIB anestezi tekniklerinin ameliyat sonrası ağrı kontrolü, morfin tüketimi, bulantı ve kusma gibi bazı yan etkiler ve hastane kalış süresi üzerine olan etkilerini omuz artroplastilerinde karşılaştırmayı amaç edindiler. Bu çalışmanın yazarları CISB anestezi tekniğinin SSIB tekniğiyle karşılaştırıldığında maliyet ve zaman kaybı gibi dezavantajları olduğunu bildirdiler. Bununla birlikte SSIB tekniği ropivakain, morfin, ketorolak ve epinefrin kombinasyonu bir kokteyle birlikte CISB tekniğinin sağladığı analjeziye iyi bir alternatif olabileceğini vurguladılar. Bu yeni çalışmanın[25] sonuçları SSIB ve LIA birlikte CISB kadar iyi bir postoperatif ağrı kontrolünü 2 gün boyunca sağladığını göstermiştir, ancak kurtarıcı morfin tüketimi bir parça daha fazlaydı. Buna rağmen SSIB alan hastalarda katater yetersizliği, katater konforsuzluğu veya katater değişimi gereksinimi gibi katater ilgili problemler yoktu. Bununla birlikte bu yeni çalışmanın bazı kısıtlılıkları vardır. Bu kısıtlılıkları şöyle sıralayabiliriz. Öncelikle çalışma retrospektif olarak düzenlendi. Lokal anesteziklerin plazma düzeyi boyun ve omuz damarlarının kazara ponksiyonu sonucu olası bir yan etki veya toksikasyon için araştırılmadı. Hastaneden taburcu olduktan sonra hastaların ağrı skorları, morfin veya analjezik tüketimleri değerlendirilmedi. Bu konuda daha fazla prospektif, geniş hasta gruplarında yan etkileri, hastane kalış süresini, yeniden kabul oranını ve hasta memnuniyetini araştıran çalışmalara gereksinim vardır. Sonuç olarak, klinik pratikte postoperatif ağrıyı kontrol etmek için multimodal analjeziklerin periartiküler injeksiyonuna olan ilgide büyük bir artış vardır. Selektif sinir blokları kolay kullanımı ve yönetimi için bu konuda bir alternatif olabilir. Omuz artroplastilerinde SSIB periartiküler analjezik injeksiyonu ile birlikte kombine edilirse CISB kadar postoperatif analjezi sağlayabilir. Ama bu

kombinasyonun etki süresi CISB tekniğininkinden önce sonlanacaktır.[1]

Bir diğer konu da eklemin kanlanması yani perfüzyon sorunudur. İyi bir perfüzyon iyi bir sağaltımla birlikte gidecektir. Rejyonal anestezi tekniklerinden birisi olan interskalen blok mükemmel bir analjezi sağlamanın yanı sıra ilgili ekstremite de daha iyi bir perfüzyon ve revaskülarizasyona yardımcı olabilir olması özelliğinden dolayı da tercih edilebilir bir yöntemdir.[26]

Cerrahi işlemin tipinin etkisi

Cerrahi işlem tipinin seçilecek anestezi ve analjezi yöntemi üzerine etkisi diğer bir önemli tartışma konusudur. Artroskopik veya işlemin açık yapılması anestezi ve analjezi gereksinimini etkilemektedir. Açık prosedürler artrosopik prosedürlere göre genelde daha fazla postoperatif analjezi gerektirir. Akromioplasti, subakromial dekompresyon, stabilizasyon, adheziolisiz (donmuş omuz serbestleştirilmesi) ve rotator kaf onarımı en sıklıkla yapılan artroskopik işlemlerdir. Açık prosedürler ise glenohumeral eklemin artroplastisi (total veya parsiyel eklem replasmanı olarak yapılabilir), açık stabilizasyonlar (LetarjeteBristow prosedürleri), açık rotator kaf onarımı ve birçok travmatik prosedürler olarak sıralanabilir (Tablo 1).

Tablo 1. Artroskopik ve açık omuz cerrahisi prosedürleri

Artroskopik	Açık cerrahi
Tanısal artroskopi	Glenohumeral eklemin artroplastisi (total veya parsiyel)
Akromioplasti (impingement-sıkışma- sendromu)	Açık stabilizasyonlar (LetarjeteBristow prosedürleri)
Subakromial dekompresyon	Açık rotator kaf onarımı
Adheziolisiz (donmuş omuz serbestleştirilmesi)	Açık travmatik prosedürler
Kapalı Rotator kaf onarımı	
Kapalı stabilizasyon	

Hem artroskopik (özellikle rotator kaf onarımı ve stabilizasyon) hem de açık omuz cerrahisi orta ve ağır postoperatif ağrı ile birliktedir.[9] Omuz cerrahilerinde anestezi ve analjezi yöntemlerinin postoperatif ağrı sağaltımı, hasta memnuniyeti ve yan etkiler üzerine olan etkileri karşılaştırılmalı olarak Tablo 2'de sunulmuştur.

SONUÇ

Omuz cerrahisinde anestezi ve analjezi tekniklerini karşılaştırdığımızda tekniğin ağrı kontrolündeki etkinliği, yan etki insidansı ve hasta memnuniyeti üzerine olan etkisini göz önüne almalıyız. Bununla birlikte bu konuda geniş hasta gruplarında, çok merkezli olarak yapılmış prospektif, randomize- kontrollü çalışmalara hala ihtiyacımız vardır.

Tablo 2. Omuz cerrahilerinde anestezi ve analjezi yöntemlerinin etkilerinin karşılaştırılması

Yöntem	Postoperatif ağrı kontrolü	Yan etkiler	Hasta memnuniyeti	Kaynaklar
Genel anestezi	Kötü	Bulantı, kusma	-	7,20
Tek atış interskalen blok (SSISB)	İyi	Daha fazla morfin	-	1,25
Sürekli interskalen blok (CISB)	Mükemmel	Ses kısıklığı, frenik sinir palsi	Yüksek	2,9,10,16,19,22
Subakromial infüzyon	Orta	Daha az	Orta	2,13,17,19
Supraskapular blok	Orta	Daha az	-	8,22
Kostoclavikular blok	Orta	Daha az	-	18,22
İv PCA	Orta	Daha az	Orta	2,15

Yazarlık katkı beyanı

Konsept ve dizayn: AE
Makale yazımı: AE
Makale revizyonu ve entelektüel katkı: AE
Danışman: AE

Yazar çıkar çatışması

Yazarların arasında potansiyel çıkar çatışması yoktur.

Destek

Bu çalışma için herhangi bir kurum ya da kuruluştan destek alınmamıştır.

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