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REVIEW
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Trigger Factors and Effects of Alzheimer's Disease

Alzheimer Hastalığının Tetikleyici Faktörleri ve Etkileri

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ABSTRACT

Alzheimer's Disease is a neurodegenerative disorder characterised by symptoms such as cognitive decline, memory loss and decreased activities of daily living. Factors that play a role in the development of this disease include genetic, environmental and neurobiological factors. The importance of genetic factors has been associated with early onset of the disease and family history. Environmental factors include lifestyle factors such as toxic metals, pesticides, nutrition, exercise and sleep patterns. Neurobiological mechanisms include amyloid cascade hypothesis, hyperphosphorylation of tau proteins, oxidative stress and inflammation. Alzheimer's Disease is diagnosed through clinical assessments and cognitive testing, and treatment options focus on symptom relief. Future research should aim to deepen our understanding of the aetiology and pathogenesis of the disease and develop more effective treatment and prevention strategies. The complex nature of Alzheimer's Disease is determined by the interaction of genetic, environmental and neurobiological factors and understanding these factors plays an important role in the management of the disease.

Keywords: Alzheimer's Disease, Genetic Factors, Environmental Risk Factors, Neurobiological Pathways.

ÖZET

Alzheimer Hastalığı, bilişsel gerileme, hafıza kaybı ve günlük yaşam aktivitelerinde azalma gibi semptomlarla karakterize edilen nörodejeneratif bir hastalıktır. Bu hastalığın gelişiminde rol oynayan faktörler arasında genetik, çevresel ve nörobiyolojik etmenler bulunmaktadır. Genetik faktörlerin önemi, hastalığın erken başlangıcı ve aile öyküsü ile ilişkilendirilmiştir. Çevresel faktörler, toksik metaller, pestisitler, beslenme, egzersiz ve uyku düzeni gibi yaşam tarzı faktörleri arasında yer alır. Nörobiyolojik mekanizmalar arasında ise amiloid kaskad hipotezi, tau proteinlerinin hiperfosforilasyonu, oksidatif stres ve enflamasyon yer alır. Alzheimer Hastalığı'nın tanısı, klinik değerlendirmeler ve bilişsel testler ile konur ve tedavi seçenekleri semptomların hafifletilmesine odaklanır. Gelecekteki araştırmalar, hastalığın etiyolojisi ve patogenezi hakkındaki anlayışımızı derinleştirerek daha etkili tedavi ve önleme stratejileri geliştirmeyi amaçlamalıdır. Alzheimer Hastalığı'nın kompleks yapısı, genetik, çevresel ve nörobiyolojik faktörlerin etkileşimiyle belirlenir ve bu faktörlerin anlaşılması, hastalığın yönetiminde önemli bir rol oynamaktadır.

Anahtar Kelimeler: Alzheimer Hastalığı, Genetik Faktörler, Çevresel Risk Faktörleri, Nörobiyolojik Yollar.

INTRODUCTION

Alzheimer's disease, first described by Alois Alzheimer, is a progressive and irreversible brain disorder that slowly destroys cognitive and memory skills, and eventually the ability to carry out the simplest tasks of daily living. In most people with Alzheimer's, symptoms first appear after age 60. It is estimated that there are currently 4 million Americans suffering from this disease. This number is expected to double in the next 20 years as the population of older adults increases. While men and women in all racial and ethnic groups are at risk for developing Alzheimer's disease, prevalence is highest in African-American and Hispanic populations. Changes in the brain can begin 20 or more years before symptoms of Alzheimer's appear. This early period represents a critical opportunity for investigating possible preventive measures that could delay or reduce the risk of developing the disorder. Characterization of the entire continuum of disease, including asymptomatic and symptomatic phases, and investigation of genetic, environmental, and biological variables associated with disease onset and progression is a current public health priority. This project seeks to identify and define factors that trigger the process of cognitive decline, leading to the symptoms of Alzheimer's and the eventual diagnosis of dementia. This is the true beginning of the disease. Understanding these factors will aid the discovery of new treatments, or the enhancement of existing ones, to improve quality of life and postponement of disease progression for the millions of individuals at risk for Alzheimer's.

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Alzheimer's Disease is a neurodegenerative disease that leads to cognitive decline, memory loss and ultimately a reduced ability to perform activities of daily living. The study of genetic, environmental and neurobiological factors involved in the development of Alzheimer's Disease is important in the treatment and prevention of the disease. In this article, we will discuss the triggering factors and effects of Alzheimer's Disease in more detail.

Role of Genetic Factors

The genetic basis of Alzheimer's Disease has clearly emerged, with onset of the disease at different ages and family history increasing the risk of the disease. There are two main forms of Alzheimer's, known as early onset (EOAD) and late onset (LOAD). EOAD is associated with genetic mutations and usually occurs in individuals under the age of 65. These mutations include changes in the APP, PSEN1 and PSEN2 genes. LOAD is associated with a genetic predisposition and usually occurs in individuals over the age of 65. The most important genetic risk factor for LOAD is various variants of the APOE gene. However, other genes are also known to influence Alzheimer's risk. For example, genes such as TREM2, CLU, CR1 and PICALM may be associated with the disease (1,2).

Impact of Environmental Factors

The effect of environmental factors on Alzheimer's Disease plays an important role in the development of the disease together with genetic predisposition. Environmental factors include toxic metals, pesticides, air pollution, nutrition, exercise, sleep patterns and social interaction. Research shows that environmental factors may increase the risk of Alzheimer's disease. For example, accumulation of toxic metals such as aluminium and mercury may play a role in neurodegenerative processes. Similarly, factors such as chronic stress, sleep disorders, and malnutrition may also negatively affect brain health and increase the risk of Alzheimer's (3-5).

Role of Neurobiological Mechanisms

The neurobiological mechanisms of Alzheimer's Disease are critical to understanding the pathology of the disease. The amyloid cascade hypothesis proposes that the deposition of amyloid-beta peptide underlies Alzheimer's Disease. Amyloid plaques can disrupt communication between nerve cells and lead to neuronal toxicity. Hyperphosphorylation of tau proteins may also contribute to the formation of neurofibrillary bundles and neuronal degeneration. In addition, other neurobiological mechanisms such as oxidative stress, inflammation, mitochondrial dysfunction and neuronal apoptosis may also play a role in the pathogenesis of Alzheimer's Disease (6-8).

Epidemiological Findings and Diagnostic Methods

Alzheimer's Disease is a global public health problem and is becoming an increasing burden with the ageing world population. The prevalence of the disease varies depending on age, gender, race and geographical location. Alzheimer's is diagnosed by clinical assessments, cognitive tests and neuroimaging methods. However, early diagnosis of the disease is still difficult and autopsy may be required for a definitive diagnosis (9-11).

Treatment Methods and Future Research

Although there is no effective treatment for Alzheimer's Disease, research has shown promising findings for the treatment and prevention of the disease. Medications, lifestyle changes, cognitive therapy and supportive care play an important role in the management of Alzheimer's Disease. Future research should aim to deepen our understanding of the aetiology and pathogenesis of Alzheimer's Disease and develop more effective treatment and prevention strategies (12-14).

CONCLUSION

The precipitating factors of Alzheimer's Disease are determined by a complex interplay of genetic, environmental and neurobiological factors. Understanding these factors can increase our knowledge of the aetiology and pathogenesis of the disease and allow us to develop more effective treatment and prevention strategies.

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Mini Review: Clicinal Strategies for Carbon monoxide Poisoning

Kısa Derleme: Karbonmonoksit Zehirlenmesinde Klinik Stratejiler

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ABSTRACT

Carbon monoxide is a type of tasteless, colorless, odorless gas that occurs as a result of incomplete combustion of organic/inorganic hydrocarbons. He is defined as the "silent killer" based on these three physical characteristics. Poisoning is seen especially in winter months due to chimney systems used in rural areas (poisoning caused by suicide and exhaust may also be seen). In a study conducted in our country, it was shown that most of the exposure to carbon monoxide gas between 1993 and 2006 was caused by stoves and water heaters without any suicidal intent. It has been stated that the affinity of carbon monoxide to the tetramer receptor region in hemoglobin is approximately 200-250 times higher than that of the oxygen molecule, resulting in hypoxia and relative anemia. Additionally, by binding to cardiac myoglobin, it causes myocardial depression and hypotension. It plays a role in the activation of platelets, causing myeloperoxidase release, high oxidative stress, inflammation, and deterioration of cellular respiration by binding and inactivating reduced cytochrome a3. Intoxication resulting from these mechanisms must be treated as soon as possible. Otherwise, life-threatening situations may occur. The first symptoms of carbon monoxide intoxication are non-specific. Physical examination findings have a limited place in diagnosis. The relationship between disease history and carboxyhemoglobin is the most reliable diagnostic tool. There is no chemical or physiological antidote for poisoning. In first aid, advanced life support steps must be applied depending on whether the patient is conscious or unconscious. Hyperbaric oxygen therapy dramatically increases patient survival and is now recommended as the gold standard treatment by separating carbon monoxide bound to hemoglobin.

Keywords: Carbon Monoxide, Hyperbaric Oxygen, Intoxication.

ÖZET

Karbonmonoksit organik/inorganik hidrokarbonların tam olarak yanmaması sonucu ortaya çıkan, tatsız, renksiz, kokusuz bir gaz türüdür. Kendine ait bu üç fiziksel özelliğe binaen “sessiz katil” olarak tanımlanmaktadır. Zehirlenme özellikle kış aylarında kırsal kesimde kullanılan baca sistemleri nedeniyle görülmektedir (Öz kıyım ve egzoz kaynaklı zehirlenmeler de görülebilmektedir). Ülkemizde yapılan bir çalışmada, 1993-2006 yılları arasında karbonmonoksit gazına maruziyetlerin çoğunun intihar amacı güdülmeden soba ve şofben kaynaklı olduğu gösterilmiştir. Karbonmonoksidin hemoglobindeki tetramer reseptör bölgesine olan afinitesinin oksijen molekülünden yaklaşık 200-250 kat daha fazla olduğu ve buna bağlı hipoksi, göreceli anemi geliştiği belirtilmiştir. Ayrıca kardiyak myoglobine bağlanarak myokardiyal depresyon, hipotansiyon, trombositlerin aktivasyonunda rol oynayarak myeloperoksidaz salımına, yüksek oksidatif strese, inflamasyona ve redükte sitokrom a3'ü bağlayıp etkisiz hale getirerek hücresel solunumun bozulmasına yol açmaktadır. Bu mekanizmaların sonucu ortaya çıkan intoksikasyonun tedavisinin en kısa sürede yapılması gereklidir aksi takdirde hastanın hayatını tehdit edebilecek durumlar ortaya çıkabilir. Karbonmonoksit intoksikasyonunun ilk belirtileri non-spesifiktir. Fizik muayene bulgularının tanıda yeri sınırlıdır. Hastalık öyküsü ve karboksi-hemoglobin arasındaki ilişki en güvenilir tanı aracı olmaktadır. Zehirlenmenin kimyasal veya fizyolojik bir antidotu bulunmamaktadır. İlk yardımda hastanın bilincinin açık ya da kapalı olma durumlarına göre ileri yaşam desteği basamaklarının uygulanması gereklidir. Hastada sağ kalımı yüksek oranda arttıran hiperbarik oksijen tedavisi hemoglobine bağlı karbonmonoksidi ayırarak günümüzde altın standart tedavi olarak önerilmektedir.

Anahtar Kelimeler: Hiperbarik Oksijen, İntoksikasyon, Karbonmonoksit.

INTRODUCTION

Carbon monoxide is a simple chemical in structure but complex in application. Structurally, it is simple, like nitrogen gas (N_2). It consists of two atoms, has the same number of electrons, and has a triple bond between its atoms. Moreover, although the boiling points of the two gases are close to each other, liquid nitrogen boils at -196 °C, and liquid carbon monoxide boils at -192 °C. The asymmetry that makes carbon monoxide a polar molecule reveals its complex structure (1,2).

Carbon monoxide occurs due to incomplete combustion of organic/inorganic hydrocarbons, and incompletely burned natural gas is also a source of carbon monoxide. Although it is a tasteless, colorless,

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odorless gas, poisoning is not noticed. He is defined as the "silent killer" based on these three physical characteristics (3). Since it is a very toxic gas, it is among the most common causes of fatal poisoning (4).

Among the 350 million population of the USA, which is among the developed countries, an average of 45 thousand people is affected by carbon monoxide poisoning every year, and 4 thousand of them die due to carbon monoxide. Mortality/morbidity data obtained from studies conducted in the USA clearly show how serious this type of poisoning has reached (5).

Although the studies conducted in our country are limited, in the study conducted in 2010, *10,154 carbon monoxide poisoning cases were identified from the records in Turkey. 39 of these cases resulted in death (6*).

OBJECTIVE

This study aims to compile pharmacotherapeutic methods that can reduce the high mortality/morbidity rates of carbon monoxide intoxication and provide treatment based on the information in the literature.

METHOD

This study has been researched, and articles relevant to studies from current medical and health databases have been examined.

RESULTS

In our country, the source of poisoning appears to be from unsuitable, unmaintained, old waste gas removal parts in homes. In addition, home accidents, which increase in winter months or windy weather due to the chimney systems used primarily in rural areas, constitute a large part of poisonings (7). A 14-year study conducted by Dokuz Eylül University Faculty of Medicine in our country between January 1993 and December 2006 revealed that most of the exposure to carbon monoxide gas was caused by stoves and water heaters, without intending suicide (8).

Pathogenesis

Since carbon monoxide naturally occurs in gaseous form, inhalation is the main route of exposure in cases of poisoning. Carbon monoxide gas inhaled by the individual quickly and easily reaches the lower respiratory tract, which begins with the larynx. Carbon monoxide is absorbed in the alveoli, which are the extreme point of respiration and are known as the air sacs. Absorbed carbon monoxide alveolar It passes through the membrane and enters the intravascular space where it binds to hemoglobin. After carbon monoxide accumulates in erythrocytes, it creates a toxic effect characterized by hypoxia (9).

The amount of gas absorbed and, therefore, the toxicity status depends on the respiratory rate (air exchanges per minute), the duration of exposure, and the carbon monoxide and oxygen concentrations (9).

Carbon monoxide toxicity is its affinity for the body protein hemoglobin. Hemoglobin is a tetramer with four oxygen binding points. Carbon monoxide's affinity for the tetramer receptor site is approximately 200-250 times greater than the oxygen molecule's (10). *This high-affinity carbon monoxide is thought to bind to hemoglobin and affect oxygen-carrying capacity by two mechanisms. The first mechanism is based on competitive inhibition of oxygen binding to hemoglobin, thus preventing oxygen from being transported and released into the tissues. This leads to a relative anemia caused by carbon monoxide, causing asphyxia or anemic hypoxia (11,12*). Secondly, carbon monoxide causes structural changes with its inhibitory effect on cellular and proteins (such as in myoglobin and hemoglobin), making it difficult to deliver oxygen to the tissues. Reduced It disrupts cellular respiration by binding and inactivating

cytochrome a3. It causes cells and tissue necrosis by reducing tissue energy production and preventing the necessary oxygen from reaching them (13).

Carbon monoxide has an affinity for cardiac myoglobin among cells, so myocardial depression and hypotension may occur due to tissue hypoxia. In addition to cardiac myoglobin, carbon monoxide also binds to linear muscle myoglobin, causing a decrease in partial oxygen pressure in muscle tissue, resulting in rhabdomyolysis, characterized by muscle pain (14,15). *Activated platelets, indirect myeloperoxidase release, high oxidative stress, and inflammation (16). The released myeloperoxidase and reactive oxygen species lead to the formation of myelin essential protein in cells. Myelin basic protein is also used as a diagnostic method (17).*

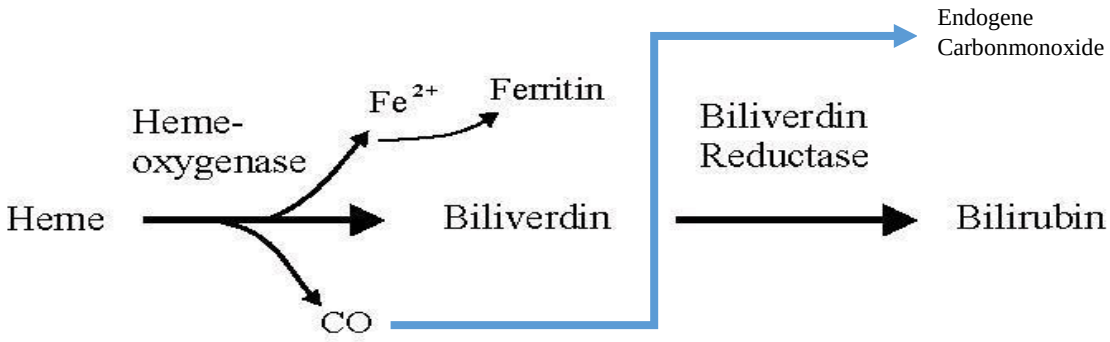

Figure 1. Formation Mechanism of Endogenous Carbon Monoxide (1).

Clinic

Carbon monoxide poisoning is called the "disease with a thousand faces," and the symptoms of poisoning are similar to viral infections. Considering that both diseases peak in the winter months, making a differential diagnosis in cases seen in these seasons becomes challenging. For this reason, disease history becomes significant in the clinic. A possible history of chimney, stove, exhaust, or workplace exposure will suggest carbon monoxide poisoning. In such an environment, breathing air containing only 0.1% carbon monoxide causes 50% of the hemoglobin in the blood to convert into carboxyhemoglobin within an hour. Half an hour more exposure to this environment makes death inevitable (18).

Symptomatology in poisoning can occur monophasically or biphasically. In the monophasic condition, patients can recover from poisoning with or without sequelae, with functional and tissue impairment. In the biphasic form, a period of coma follows, making the patient and treatment difficult. There is an interval period. This is a pseudo-period in which the patient's clinical condition remains good, and his consciousness remains temporarily clear. After this pseudoperiod, which can mislead the physician, the patient's clinical condition deteriorates rapidly, and the patient dies (19).

Since the poisoning mechanism is based on blood proteins such as erythrocytes and every organ requires blood supply, all organs in the clinic are affected by this poisoning. However, the main symptoms are cardiovascular and neuropsychiatric since the brain and heart are organs with high oxygen consumption (20). The brain regulates its respiration according to the carbon monoxide concentration in the blood. Therefore, people who are unaware they are breathing carbon monoxide will not notice anything wrong. At the same time, he will continue to breathe normally until he loses consciousness. In case of death, the skin becomes pinkish at autopsy, and the blood is bright red due to carboxyhemoglobin (21).

Although the typical sign of poisoning is the appearance of cherry red lips, this is a non-specific sign. According to the observations made by the Düzce Faculty of Medicine, patients who experienced acute poisoning:

Respiratory system: Exercise dyspnea, signs of upper respiratory tract infections

Nervous system: Lethargy, confusion, depression, hallucination, agitation, syncope, coma, memory and gait disturbance, dizziness, headache

Clinical findings such as chest pain, sinus tachycardia, and palpitations have been observed. It should not be overlooked that the symptoms are mainly neuropsychiatric and cardiovascular and are not specific(22).

However, since carboxyhemoglobin levels may be at values that may mislead the physician, the disease history should support the results. What is important here is the blood exposure time, exposure amount, respiratory rate, and the amount of oxygen in the environment. Carboxyhemoglobin levels may decrease further in the long term. Low carboxyhemoglobin levels can also lead to poisoning and put the patient's life in danger (9).

Diagnosis

Poisoning is often confused with viral upper respiratory tract disease, and when acute symptoms are considered, it is seen that the patient does not have any specific findings. For this reason, the most crucial point in diagnosis is the history of poisoning (5).

During the physical examination, the patient had cherry red lips, pale skin, and retinal Flame burn in the eye due to hemorrhage, the retinal bright red color of the veins (a sensitive early finding), papillary edema, loss of vision in both eyes simultaneously, pupillary Findings such as mydriatic may be observed. However, these are also non-specific findings (23,24).

In cases of poisoning, oxygen saturation can be measured with a pulse oximeter. However, since the measurement deals with the respiratory system, it may be expected in patients whose respiratory system is unaffected. It may give misleading results to the physician. For this reason, using a pulse oximeter in diagnosis may cause possible poisoning to be overlooked. Also, pulse oximeter does not provide information about carboxyhemoglobin and oxyhemoglobin levels. The primary mechanism of poisoning is oxygen transport in hemoglobin. Since carbon monoxide is the inhibitor, correct diagnosis requires measuring carboxyhemoglobin levels (25,26).

Carboxyhemoglobin in poisoning is diagnosed from a heparin-treated blood sample (arterial or venous); arterial blood is preferred (27). Symptoms, which even the individual can hardly notice, begin at a concentration of 3%, and the findings become more severe when they reach 10%. It is realized that physiological abnormalities might occur. However, applying this test to smokers after smoking may give misleading results. In cigarette addiction, the carboxyhemoglobin value can reach approximately 5.5% for 20 cigarettes (1 pack) per day. (5,28). While the carboxyhemoglobin level is around 1% in non-smoking individuals , this value is up to 15% in patients with a history of heavy smoking (29). *In general, carboxyhemoglobin levels below 40% are not associated with coma or death. A carboxyhemoglobin concentration of 40% and above is observed in high toxifications. In 20% of cases, breathing becomes more complex, and the patient suffers headaches and dizziness. A carboxyhemoglobin level of 5% is the concentration at which oxygen transport is inadequate; hemolytic anemia might occur. The first signals that treatment should be started should be received here (30).*

Considering all those symptoms and values, the patient has comorbid serum lactate increment and metabolic abnormalities. If there is acidosis, it should be regarded as that the patient may be exposed to long-term carbon monoxide (25).

Hemogram tests for immunity and tissue hypoxia, liver function tests for carbon monoxide metabolism, muscle and cardiac enzyme tests to see the effect it creates by binding to myoglobin, and urinalysis, a measure of blood, should be requested from the laboratory. In case of clinical suspicion, chest radiography, computerized brain tomography, magnetic resonance and electrocardiogram methods should be used. However, after these tests are conducted, the time it takes for the results to outcome should be taken into consideration. The patient should take necessary symptomatic treatment (31).

Treatment

Treatment can proceed symptomatically. If hypotension occurs, the patient and the serum isotonic are placed in the Trendelenburg position. Infusion is made, and vasoconstrictor drugs can be used if necessary. If there is persistent hypotension, noradrenaline treatment should be started in the patient. Patients with neurogenic seizures should be treated with benzodiazepine. If there is no response or the seizure recurs, other antiepileptics, such as barbiturates, are added to the treatment. Barbiturates should be used with caution as the somnolence threshold level will be lower than benzodiazepines. If fever develops due to activation of the immune system, intravenous paracetamol should be started as an antipyretic. Possible use of NSAIDs will cause constriction in the afferent artery in the kidney, which will reduce blood flow in the kidney, thus causing acute renal failure (5).

Protocols that significantly increase patient survival. The first is hyperbaric oxygen therapy, and the other is oxygen intake through a mask.

Oxygen therapy with mask: 4-6 hours until the patient's clinical findings improve or until the COHb level drops below 5% in mild/moderate poisoning. In severe poisoning, it should be given until the COHb level drops below 2% (32).

Hyperbaric oxygen therapy: *Separation of carbon monoxide bound to hemoglobin is impossible with pure oxygen gas; therefore, high-pressure oxygen must be used in treatment. Hyperbaric oxygen therapy can quickly improve symptoms and reduce deaths due to poisoning when administered within the first 6 hours. In addition, it is a more effective method than normobaric oxygen therapy in preventing neuropsychiatric symptoms that occur with chronic toxic effects as well as in the acute period (33). Hyperbaric oxygen therapy should be preferred in patients experiencing loss of consciousness (34). Hyperbaric oxygen therapy has shown its success even in neuropsychiatric symptoms that appeared after three weeks (35).*

CONCLUSION

The first symptoms of carbon monoxide poisoning are nonspecific. Physical examination findings are limited in diagnosis. The patient’s epicrisis is the most trusted diagnostic tool. When poisoning is suspected, the COHb level in the blood should be measured as soon as possible. The source of carbon monoxide in the patient's environment taken by ambulance should be identified, and the source should be eliminated. The patient should be provided with oxygen support, and hospitalization should continue. Providing oxygen support to a patient brought to the emergency room by ambulance without the knowledge of the physician causes low carbon monoxide levels in the blood. In this case, the physician must obtain the necessary information from the healthcare professional who provides first aid. Otherwise, disruption of the treatment is inevitable (36,37). There is no chemical or physiological antidote for poisoning. The mechanism of toxicity should be aimed at separating carbon monoxide from protein (38).

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LETTER TO THE EDITOR
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Use of Nanotechnology in Medical Biochemistry

Tıbbi Biyokimya'da Nanoteklojinin Kullanımı

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Dear Editor,

Nanotechnology has an important place in the field of biochemistry/chemistry. The utilisation of nanotechnology in this field is of great importance. We would like to emphasise the importance and effects of nanotechnology in the field of chemistry and highlight the recent developments in this field.

Nanotechnology has become an important focus of interest in the field of chemistry in recent years. This technology enables the design and production of new materials by controlling matter at the atomic or molecular level. In particular, the unique physical, chemical and optical properties of nanomaterials lead to revolutionary applications in many fields.

Research shows that nanotechnology has great potential in various fields such as medicine, electronics, energy storage, environmental protection and materials science. For example, more effective and less invasive methods can be developed in cancer treatment with the use of nanoparticles. In addition, energy technologies such as solar cells and battery storage systems can be made more efficient thanks to nanotechnology (1-5).

In this context, the role and impact of nanotechnology in the field of chemistry should be understood more comprehensively. More research and co-operation is needed to fully exploit the potential of this technology and to translate it into industrial applications.

I would like to ask you to publish articles in the field of nanotechnology to bring this important topic to a wider audience and to encourage scientists to do more work in this field.

Best regards.

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RESEARCH ARTICLE
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Verbascum pulverulentum Vill. Ekstraktının Yetişkin İnsan Dermal Fibroblast (HDFa) Hücre Hattı Üstündeki Yara İyileştirici Etkilerinin Araştırılması

Verbascum pulverulentum Vill. Ekstraktının Yetişkin İnsan Dermal Fibroblast (HDFa) Hücre Hattı Üstündeki Yara İyileştirici Etkilerinin Araştırılması

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ÖZET

Kemoterapi kanserin tedavisinde sıklıkla kullanılan yöntemler arasında yer alır ve kanserli hücrelerin gelişmesini ve çoğalmasını önlemek amacıyla kullanılır. Kemoterapi kanserli hücrelerin çoğalmasını ve gelişmesini önlerken normal hücrelere de zarar vermektedir. Kemoterapinin bu sitotoksik zararından en fazla etkilenen oral mukoza epitel hücreleridir. Oral mukoza epitel hücreleri diğer hücrelere göre daha hızlı bölünebilme özelliğine sahip olduğu için kemoterapik ajanlar oral mukoza hücrelerinin büyüme ve olgunlaşmasını baskılayarak ağız ve boğazdaki primer mukozal bariyeri bozmaktadır. Bunun sonucu olarak gelişen oral mukozit mukoza bariyerinde bozulma, epitel hücrelerde zayıflama, eritem, ödem, kanama, sık ülserasyonlar, ses kısıklığı, konuşma güçlüğü, çiğneme ve yutma güçlüğü ile karakterizedir. Mukozit, tüm sindirim sistemini etkileyebilen, ağrı, ağız ülseri, şişkinlik, kusma, ishal ve peristaltizm bozukluklarına neden olan mukozanın inflamatuar bir değişikliğidir. Mukozit, lokal ve sistemik enfeksiyon insidansını artıran, yaşam kalitesini düşüren, radyasyon dozu ve kemoterapide sınırlayıcı bir risk faktörüdür. Mukozit hasarı nedeniyle, lokal ve sistemik enfeksiyon riskinin artar, yaşam kalitesi düşer, tedavi maliyetini artar, radyasyon dozu ve iletiminde sınırlamaya neden olur. Bu çalışmada, *Verbascum pulverulentum Vill.* ekstraktı ile geliştirilecek olan aday ilaç molekülü sayesinde öncelikli olarak kemoterapi sonucu meydana gelen bukkal mukozit yaraların iyileşmesinin hızlandırılması, yara iyileşmesi hızlandığından yaraların açık kalması sorununun azalması ve patojen mikroorganizmalar ile enfekte olma olasılıklarının azalması, bunun neticesinde de kemoterapi hastalarında mukozit prevalansının düşürülmesi amaçlamaktadır.

Anahtar Kelimeler: Epitel Hücresi, Hücre Kültürü, *Verbascum pulverulentum Vill.*, Yara İyileşmesi.

ABSTRACT

Chemotherapy is among the methods frequently used in the treatment of cancer and is used to prevent the development and proliferation of cancerous cells. While chemotherapy prevents the proliferation and development of cancerous cells, it also damages normal cells. Oral mucosal epithelial cells are most affected by this cytotoxic damage of chemotherapy. Since oral mucosa epithelial cells have the ability to divide faster than other cells, chemotherapeutic agents suppress the growth and maturation of oral mucosa cells and disrupt the primary mucosal barrier in the mouth and throat. Oral mucositis that develops as a result is characterized by deterioration in the mucosal barrier, weakening of epithelial cells, erythema, edema, bleeding, frequent ulcerations, hoarseness, difficulty in speaking, difficulty in chewing and swallowing. Mucositis is an inflammatory change of the mucosa that can affect the entire digestive system, causing pain, mouth ulcers, bloating, vomiting, diarrhea and peristalsis disorders. Mucositis is a risk factor that increases the incidence of local and systemic infection, reduces quality of life, and limits radiation dose and chemotherapy. Due to mucositis damage, the risk of local and systemic infection increases, the quality of life decreases, the cost of treatment increases, and it causes limitations in radiation dose and delivery. In this study, Verbascum pulverulentum Vill. thanks to the candidate drug molecule to be developed with the extract, it is primarily aimed to accelerate the healing of buccal mucositis wounds that occur as a result of chemotherapy, to reduce the problem of wounds remaining open as wound healing is accelerated, and to reduce the possibility of infection with pathogenic microorganisms, and as a result, to reduce the prevalence of mucositis in chemotherapy patients.

Keywords: Cell Culture, Epithelial Cell, *Verbascum pulverulentum Vill.*, Wound Healing.

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GİRİŞ

Yara, vücuda gelebilecek bir yaralanma sonucu cildin epidermisinde hasar oluşması ve derinin normal anatomisinin ve fonksiyonlarının bozulması olarak tanımlanır. Yara iyileşmesi, kazayla veya kasıtlı olarak meydana gelen travma sonrası derinin bütünlüğünü korumak için önemli bir fizyolojik süreçtir (1).

Yara iyileşme süreci dinamik bir süreçtir (2). Yara iyileşmesinde keratinositler, endotel hücreleri, fibroblastlar ve inflamatuar hücreler ile sitokinler, büyüme faktörleri ve hücre dışı matriks dâhil tüm hücre tipleri yer alır. Ayrıca normal yara iyileşmesinin gerçekleşmesi için bu hücre tiplerinin, büyüme faktörlerinin ve enzimlerin etkileşiminin yüksek düzeyde entegre olması gerekir (3).

Türk geleneksel tıbbında Verbascum türlerinin yaprak, çiçek ve bütün toprak üstü kısımları yaraların tedavisinde yara kurutucu olarak kullanılmaktadır (4). Verbascumun birçok türünün toprak üstü kısımları anal fistül tedavisinde kullanılmaktadır. Kurutulmuş ve toz haline getirilmiş yaprakları yaralar için kurutucu olarak kullanılmış, kaynatılan yapraklar karın ağrısı ve bronşit için çay olarak içilmiştir (5). Verbascum L. türlerinin çiçekleri ürogenital organlardaki kaşıntılı durumlarda kullanılmıştır (6). *Verbascum pulverulentum vill.* türü ile ilgili yeterli çalışma olmayışı yeni çalışmaları yapılması hususunda önem arz etmektedir.

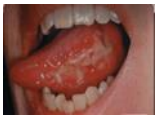
Kemoterapi, hızla bölünerek ve büyüyerek çoğalan kanser hücrelerinin büyümesini durduran veya yavaşlatan bir tedavi yöntemidir. Kanseri tedavi etmek (kür sağlamak) ve tekrar etme riskini azaltmak amacıyla kullanılabileceği gibi, ağrı veya başka şikayetlere yol açan tümörlerin küçültülmesi amacıyla da kullanılabilir (7).

Kanserin birçok çeşidinde kemoterapi kullanılmaktadır. Çoğu zaman, kanser tedavisinde kemoterapiden önce veya sonra cerrahi tedavi ve/veya ışın tedavisi (radyoterapi) yapılmaktadır. Cerrahi veya radyoterapi öncesinde, tümör boyutunu küçültmek için kemoterapi önerilebilmektedir. Kemoterapi büyüyen ve bölünen hücreleri öldürdüğünden bu tür özellikleri olan normal hücrelere de zarar verebilir. Bu tür hücreler kemik iliği, sindirim ve üreme sisteminde ve saç foliküllerinde bulunduğu için yan etkiler daha çok bu bölgelerde görülür. Bu yan etkiler; yorgunluk ve kansızlık, mikrop bulaşması, infeksiyon, kanama problemleri, bulantı ve kusma, saç dökülmesi, ağız içi ve yemek borusu yaralar, ishal, kabızlık, cilt ve tırnaklara etki, iştahsızlık, cinsel fonksiyon bozukluğu gibi birçok yan etkisi bulunmamaktadır. Oral Mukozit kanser tedavisinin yaygın ve zayıflatıcı toksisitelerinden biridir (8).

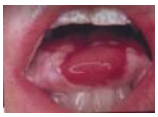
Oral mukozitin klinik ve ekonomik sonuçları genellikle mukozitin ileri evrelerinde görülmektedir. Ciddi mukozit, hastaların ağız boşluğunda ve/veya boğazlarında şiddetli ağrı yaşamalarına neden olmaktadır ve bu durum bir yaradan çok daha fazla hasara sebep olabilmektedir (9).

Yeterince beslenemeyen hastalarda kilo kaybı, dehidratasyon, mukozada ülserasyon, sıvı-elektrolit dengesizliği gelişebilmekte ve total parenteral beslenme (TPB) başlanabilmektedir (10). Tedavi edilemezse, hastaların hastanede yatış süreleri uzamakta, tedavi maliyetleri artmakta ve yaşam kaliteleri bozulmaktadır (11).

Genel olarak yara iyileşmesi senkronize olmuş bir olay olmakla beraber hemostaz, inflamasyon, proliferasyon ve yeniden şekillenme aşamalarından oluşmaktadır (12). Yara iyileşmesinde fibroblastlar, ECM proteinleri, keratinositler, TGF-β,trombosit kaynaklı büyüme faktörü-CC (PDGF-CC, vasküler endotelyal büyüme faktörü (VEGF) ve hepatosit büyüme faktörü (HGF) rol alan ana yapılardır (13). Bu çalışamamızda fibroblastların yara iyileştirmesindeki etkisinden yararlanarak bukkal mukozit tedavi edilmesi ve önlenmesi üzerine çalışmalar gerçekleştirilecektir.



Şekil 1.



Şekil 2.

Şekil 3.

(Şekil 1-2 de kemoterapiye, şekil 3'te radyoterapiye bağlı bukkal mukozit yaraları görülmektedir.)

Van Çaldıran sellik köyünde Yapılan bir etnobotanik çalışmada yöre halkının *Verbascum pulverulentum Vill.* (Yöre halkı deyişiyle mevujark) bitkisinin toprak üstü kısmının kurutulup toz edildikten sonra yaraların üzerine sürüp kullandıklarını ve bir hafta süreyle uygulama yaptıklarından sonra yarada gözle görülür sonuçlar alındığını ifade etmişlerdir.

Çalışmanın amacı *Verbascum pulverulentum Vill.* ekstraktının yara iyileştirici etkilerinin hücre kültürü ortamında araştırılmasıdır. Elde edilen veriler doğrultusunda da ileride bukkal mukozitte kullanılabilecek bir aday ilaç molekülü elde edebilmektir. Elde edilecek bu aday ilaç molekülünün etkileri sayesinde de hastaların refah seviyeleri artabilecek, kemoterapi veya radyoterapi gören hastalarda ağız ve boğazda oluşan yaraların iyileşmesi hızlanabilecek ve yara iyileşmelerinin hızlanması halinde bukkal mukozit görülme durumu azalabilecektir.

YÖNTEM

Verbascum pulverulentum Vill. Bitkisinin Toplanması ve Kurutulması

Verbascum pulverulentum Vill. Mayıs 2022'de Van Çaldıran Sellik Köyü civarı 2050m rakımda (39.127641,43.898286) toplandı ve teşhis edildi. Güneş görmeyen, oda sıcaklığında kurutuldu.

Verbascum pulverulentum Vill. Bitki Ekstresinin Hazırlanması

Gölgede kurutulan bitki örneği çiçekli gövdesi öğütücü ile toz haline getirildi. 150 g toz edilmiş *Verbascum pulverulentum Vill.* soxhlet apareyinde etanol ile tüketildi. Elde edilen ekstre rotavaporda alçak basınç altında yoğunlaştırılıp etanol ekstresi hazırlandı.

HDFa Kültürü

Bu hücre hattının kültüre edilmesinde DMEM (Dulbecco's Modified Eagle Medium), FBS (Fetal Bovine Serum), Penisilin – Streptomisin, amphotricin B (Life 26 Technology Gibco 15240-062), %1 L-Glutamine (Life Technology 25030-081) maddeleri kullanıldı.

MTT sitotoksisite Testi

MTT [3- (4,5- Dimethyldiazol-2-yl)-2,5 Diphenyl Tetrazolium Bromid] tozu: Sigma Aldrich, No: MKBR4419V Toz halinde MTT ürününden solüsyon hazırlama işlemi için öncelikle 5 mg toz halinde MTT tartıldı. Akabinde 1 ml arındırılmış PBS ilavesi yapıldı. Çözünme işlemi tamamlandıktan sonra 0.22 µm çapında porlara sahip filtreler kullanılarak sterilize edildi. MTT çözeltisi olarak kullanılan DMSO (dimethyl sulfoxide) W29A01596 numaralı Sigma Aldrich ürünüdür.

Verbascum Pulverulentum Vill. Ekstraktlarının oluşturduğu sitotoksisite düzeyini ölçme amacıyla MTT testi yapıldı. (Çizelge 3.1). Ekim sonrasında plate tabanına yapışan hücrelerin üzerinde yer alan besi ortamı alındı. *Verbascum Pulverulentum Vill.* ekstraktlarını içeren besi ortamları flasklara ilave edildi. Etken maddelerini içeren ortamlarda hücrelerin 24 saat süreyle maruz kalmaları sağlandı.

İn-vitro deneyde kullanılan dozlar

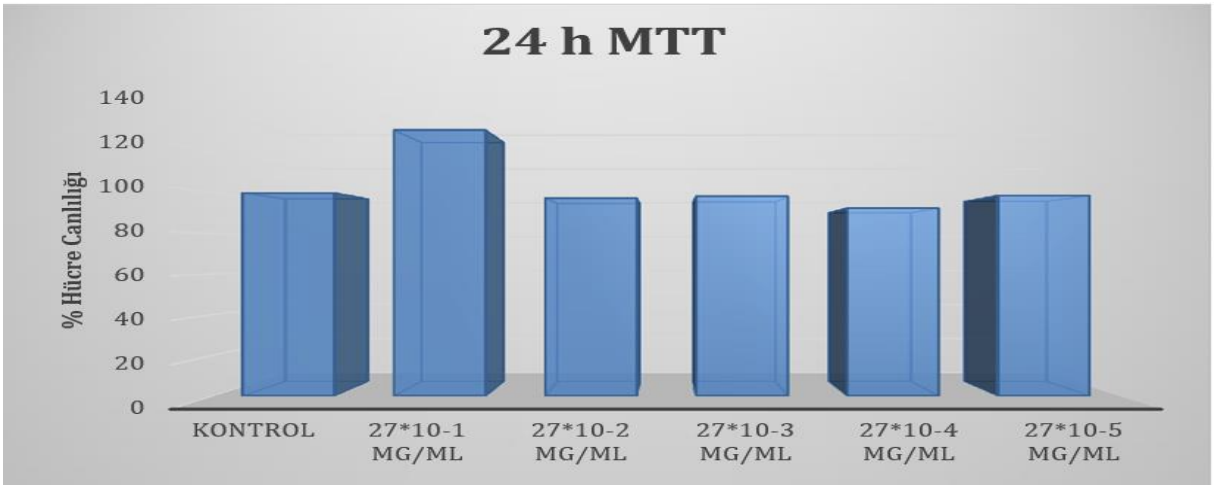
Deney grupları	Dozlar
Kontrol	-
Verbascum Pulverulentum Vill. Ekstraktı	$27*10^{-1}$ mg/ml
Verbascum Pulverulentum Vill. Ekstraktı	$27*10^{-2}$ mg/ml
Verbascum Pulverulentum Vill. Ekstraktı	$27*10^{-3}$ mg/ml
Verbascum Pulverulentum Vill. Ekstraktı	$27*10^{-4}$ mg/ml
Verbascum Pulverulentum Vill. Ekstraktı	$27*10^{-5}$ mg/ml

Tüm bu konsantrasyonlarda yapılan uygulama işleminin yanı sıra, kontrol olarak hazırlanan kuyucuklara kullanılan maddelerin hazırlanmasında kullanılan çözücüden de aynı oranda uygulandı. Kullanılan her bir etken maddenin farklı konsantrasyonlarda uygulama işlemi kapsamında her bir madde için en az 6 kuyucuk kullanıldı. Maruziyet süresi sonunda hücreler üzerinde yer alan besiyeri 90 µl'ye tamamlandı. Akabinde daha önceden hazırlanmış olan MTT solüsyonu (5mg/ml) kuyucukların her birine 10 µl ilave edilerek kuyucukların hacimleri 100 µl'ye tamamlandı. Bunun ardından hazırlanan plateler 37°C'de, %5 CO2 'li inkübatörde 4 saat bekletildi. Bu işlemin sonundan kuyucuklarda yer alan sıvı boşaltılarak yerine 100 µl DMSO ilave edildi. DMSO ilavesi ardından spektrofotometre ile 570 nm dalga boyunda okuma işlemine geçildi.

BULGULAR

Hücre Kültürü MTT Testi

24 saat ilaç maruziyetinden sonra kültür kaplarına MTT solüsyonu eklenerek hücre canlılığı incelenmiştir. Elde edilen veriler analiz edildikten sonra aşağıda sunulmuştur.



Şekil 1. HDFa hücreleri için % canlılık oranları- MTT test grafiği

Şekil 1'de HDFa hücrelerinin 24 saatlik ilaç maruziyeti sonrası canlılık oranı MTT testi yardımıyla hesaplandı. Bu amaçla verbascum pulverulentum'un 27*10-1 mg/ml, 27*10-2 mg/ml, 27*10-3 mg/ml, 27*10-4 mg/ml, 27*10-5 mg/ml ve bu dozların kombinasyonları HDFa hücrelerine uygulandı. Tüm grupların anlamlılık sonuçları kontrol grubuyla karşılaştırılmıştır. Alınan sonuçlarımıza göre 27*10-1 grubu en yüksek canlılığı gösterdi. Elde edilen verilere göre *verbascum pulverulentum vill.* ektraktının 27*10-1 mg/ml dozunun ilave edildiği grup kontrol grubuyla karşılaştırıldığı zaman %130,8693631 oranında bir çoğalma gerçekleştiği görülmüştür.

TARTIŞMA ve SONUÇ

Kemoterapi, kanser tedavisinde sıklıkla kullanılan etkili bir yöntemdir. Bununla birlikte, kemoterapi tedavisine bağlı olarak bir dizi yan etki ortaya çıkabilir ve bunların arasında mukozit de bulunur. Mukozit, mukozal dokunun iltihaplanmasıyla karakterize olan bir durumdur (14). Mukozit gelişiminde, kemoterapi ilaçlarından kaynaklanan toksik etkiler, mukozal dokuda hücre ölümüne ve iltihaplanmaya neden olur. Kemoterapi ilaçları, hızla bölünen hücreleri hedef alırken, sağlıklı hücrelere de zarar verebilir (15).

Mukozitin semptomları genellikle kemoterapi tedavisi başladıktan sonra birkaç hafta içinde ortaya çıkar. Ağız ve mukozal bölgelerde görülen inflamasyon ve ülserasyonlar, teşhis için önemli bulgulardır. Ayrıca, bazı ilaçlar ve tedavi protokollerinde mukozit önleyici ilaçların kullanılması da yaygın bir uygulamadır (16).

Mukozitin yönetimi, semptomların hafifletilmesini, yaraların iyileştirilmesini ve hasta konforunun sağlanmasını hedefler. Bu amaçla, ağrı yönetimi için analjezik ilaçlar, topikal anestezikler ve oral hijyen ürünleri kullanılmaktadır. Yaraların iyileştirilmesi için topikal ajanlar ve ağız çalkalama solüsyonları kullanılmaktadır. Ancak bu ilaçlar mukozitin iyileştirilmesinde yeterli düzeyde değildir (17).

Bu çalışmada amacımız mukozitin en kısa sürede iyileşmesini sağlayacak bize yeni ilaç geliştirilmesine öncü olmaktır. Çalışmamız esnasında hücre canlılığını takip etmek için MTT analizi yöntemini kullandık. Biz çalışmamızda ucuz, hızlı, etkili, kolay kullanımlı, güvenilirliği oldukça yeterli ve dünya çapında yaygın kullanıma sahip olduğu için MTT analizi yöntemini kullandık. MTT analiz sonuçlarımıza göre hücrelerin canlılık düzeylerinin arttığı bulunmuştur. Buna göre *Verbascum pulverulentum vill.* 27*10-1 mg/ml verilen grupta kontrole göre anlamlı bir biçimde hücre çoğalmasında artma gözlenmiştir

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